The Empirical Application of Real Options and Corporate Competencies to Research and Development in the Pharmaceutical Industry

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The Faculty of Economics, Business Administration and Information Technology of the University of Zurich hereby authorizes the printing of this dissertation, without indicating an opinion of the views expressed in the work.

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Chairman of the Doctoral Board: Prof. Dr. Josef Zweimüller

To my grandparents, Rina and Severino

Preface

The complex processes involved in researching, developing and launching a drug onto the marketplace poses pharmaceutical companies with a unique set of challenges. Pharmaceutical innovation is a long, risky and expensive process involving research and development with often unforeseeable consequences within a highly regulated competitive environment. As well as this, the positioning and launch of a drug product requires very specific marketing skills and strategic competitive tactics. In the context of the innovation process described above, this study aims at analyzing the best financial valuation and strategic practices required in order to develop and commercialize a new pharmaceutical product.

The Introduction describes the unique characteristics of the pharmaceutical business, which is by definition dominated by the uncertainty of research and development activities. It will further analyze the inadequacy of some valuation methods currently employed in the industry. The traditional capital budgeting approach based on net present value fails to capture the managerial ability to learn and respond in a flexible way to future events. Conversely the real option method integrates managerial flexibility and the options embedded in corporate decisions into the valuation process.

Chapter 1 deals with the concept of real options in a discrete setting. Various attempts have been made in literature and by practitioners to apply valuation with real options in the pharmaceutical industry. The main contribution of this chapter lies in the development of the model and in the calibration of the parameters used to model various examples of real options. The model setting assumes a multiperiod binomial model under real-world probabilities. A risk adjusted discount rate evolves according to the interaction between technical and market risk during the development phase. Managers of the life science industry have experience with peak sales predictions and sales curves identified by those peaks. Two kinds of volatility parameters are therefore considered in business practice: the volatility of peak sales predictions and the volatility of the entire sales curve. The volatility of peak sales predictions is estimated

based on real portfolio data for specific disease areas. Conversely, research on the volatility of the entire sales curve is performed using managers' views based on their market knowledge.

Chapter 2 analyzes real option models in continuous time with strategic competitive interactions. After a critical literature review, Weeds' (2002) model is selected as a suitable framework for the pharmaceutical case. The results obtained by the application of the model are then analyzed using specific business considerations related to the competence factor. The main contribution of this chapter is a generalization of Weeds' model to better represent the cash flow dynamics affected by patent expiration using a Geometric Brownian motion underlying a firm's cash flow. In this context a Geometric Brownian with two drifts regimes is necessary to represent the cash flow dynamics of a drug before and after patent expiration. The results show that a change in the drift has a significant impact on a firm's value. This implies that the utilization of the Weeds' model, assuming a unique drift, can largely overstate firm value. A model extension is also developed so as to address other Weeds model's limitations such as the assumption of exogenous cash flows being independent from the random time of discovery.

Chapter 3 provides the empirical estimate of the competence factor, which is regarded as a key driver in the decision to enter in a strategic alliance in the pharmaceutical industry. Empirical estimates based on the Logit model find that an increase in the competence factor implies a significant decrease in the probability of signing a deal. These results are consistent with what is observed in real business practice. A firm's main driver behind strategic decisions to pursue alliances is determined by the level of specific knowledge in a given disease area. A high level of knowledge makes the cooperative approach less favorable. In the pharmaceutical business a key strategic decision refers to the possibility to maximize market share either by being a market leader or by setting up cooperative alliances. In this respect an important role is played by knowhow and competences developed over time by experience and organizational learning. The idea that the competitive advantage derived from internal competencies makes a strategic alliance less favorable has been supported by the empirical evidence in this chapter.

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Contents

Acronyms used

CVM	Cardiovascular
EMEA	European Medicine Control Agency
FDA	Food and Drug Administration
IA	Interim Analysis
ID	Infectious Diseases
IND	Investigational New Drug application
LCM	Life Cycle Management
LOE	Loss of Exclusivity
MA	Marketing Authorization
NDA	New Drug Application
NM	New Molecule
P	Probability to Approval
PIE	Parallel Indication Expansion
PoC	Proof of Concept
PoS	Probability of successfully moving to the next Phase
RESP	Respiratory
SM	Small Molecule
TA	Therapeutic Area
TPP	Target Product Profile

Introduction: Valuation methods in the pharmaceutical industry

Drug development

The Pharma pipeline consists of a number of molecules undergoing rigorous research and development processes to assess their future potential as marketable pharmaceutical drugs. These sequential phases are common to all Pharma companies which, in order to bring a compound on the market, need to go through a clear legal path which is regulated by a regulatory authority. The primary aim of such regulations is to ensure that the marketed drugs have an adequate safety profile.

According to Herrling (2005) the processes that such molecules must undergo on their path to market include three discovery phases during the research process, phases D1 to D3, and five phases in development. The latter phases include preclinical development, clinical development phase 1, phase 2 and phase 3 and, finally, registration and regulatory approval phase.

The discovery research responds to a company's strategic priority in terms of selected therapeutic areas. The portfolio of therapeutic areas needs to be constantly monitored because the value of new discoveries changes over time and is affected by variables such as competition, product innovation or price changes. For example, the pharmaceutical industry is currently focusing on specialties areas such oncology, immunology, and neurodegeneration. Those are therapeutic areas that are also driven by the aging population and for which one can expect a relatively low rate of innovation in the short term.

A company's focus of research is determined by a variety of factors. These include theories of therapeutic differentiation where the medical benefit of a new drug is valued against existing medical practice or the evidence of data (i.e. confidence in the efficacy and safety

profile) in order to ascertain whether a new scientific hypothesis is feasible.

Research

Research starts with the discovery of an active compound which is a compound that can modify a biological process. At this initial stage, there are two fundamental steps. The first involves the identification of the target molecule and the second the identification of the "lead compound".

Based on the work of Herrling (2005) the target molecule relates to the molecular location in the human body that, interacting with the drug compound can prevent or modify the course of a disease. The target molecule differs according to the specific disease: it could be a defective protein, a virus in the case of an infectious disease, a lack of hormones in a metabolic disease such as diabetes or a biochemical signal that does not work properly. The identification of the target molecule is not an easy task, especially for complex diseases where it is particularly challenging to identify the key drivers that can interact with the drug compound.

According to Grossmann (2003), the drug compound will predominantly trigger two kinds of interactions or signals. These are antagonist signals, which employ a blocking mode of action, or agonist signals which conversely employ a stimulating mode of action.

According to the role that a target molecule plays in the disease, the effects of the drug compound can go from healing the disease to acting only in the short term on specific aspects of the disease. For example, for viruses responsible for certain infections the target will play an early role, while it plays a later role in cases such as the lack of dopamine production in the brain of a patient with Parkinson's disease.

Once the target molecule, generally a protein, has been selected, phases D1 and D2 deal with the so called "ligand screening". Based on the work of Herrling (2005) during D1, the circa 1 million chemical compounds that constitute a company's compound library are considered. This stage involves identifying which compounds interact the best with the target molecule and have the capability to impact on the disease; these are the so-called "lead" compounds. These lead compounds are further modified to optimize certain characteristics of solubility and metabolic properties, a process referred to as the "lead optimization phase". Possible side effects are then tested in vitro and animals. During phases D2 and D3 the medical benefit of the potential drug is assessed in comparison to the existing standard of care.

By the end of phase D3 the optimized compound presenting an "ideal fit" with the dis-

ease target is patented before moving into the development phase. At the same time other promising lead compounds that exhibited impact on the disease are kept as a backup to the main compound throughout development progression. Should the main compound fail at any stage, other potential candidates would still be available. The duration of D1-D3 phases is about two years.

Development

Preclinical trials

The preclinical phase represents the last phase prior to tests in humans. The lead optimized compound is extensively tested to verify the absorption, metabolism and elimination properties of the drug, or its pharmacokinetics, in addition to its toxicity. This research is conducted on at least two species of animals, usually rodents and non rodents, monkeys, dogs or cats. The goal is to verify if the compound can be safely tested later on humans without causing toxic reactions. Based on http://it.wikipedia.org/wiki/Farmacocinetica the appropriate route of administration of the compound, through either enteral (oral, sublingual, rectal) or parenteral, is also identified during this phase.

Due to the rigour associated with this phase, preclinical trials present a high rate of failure with only about 1 in 1000 of the compounds able to move successfully to the next phase as stated by Adams and Van Brantner (2003). For the successful candidates, for which a certain level of safety is determined, the target drug candidate undergoes three phases of clinical testing in humans.

Explorative – phases 1 and 2

Based on Bodgan and Villiger (2007) before starting human drug trials, an Investigational New Drug application (IND) must be approved by the Food and Drug Administration (FDA) in the USA. In Europe the European Medicine Control Agency (EMEA) is the approving committee concerned with drug tests in humans.

In phase 1 the same elements used in preclinical trials are assessed in humans. Once more, studies on pharmacokinetics, pharmacodynamics and bioavailability are conducted but for the first time on humans rather than animals.

According to Adams and Van Brantner (2003) in phase 1, the effects of the drug are tested on a small group of healthy volunteers (less than 100) to test for safety, toxicity and dose ranges.

Side effects are also tested to look for the potential effects of the drug on other, non-target organs leading to undesired effects.

Further modifications of the molecule are made both to the chemical composition and to the production process. Thereafter the compound is again exposed to to all preclinical and clinical tests. Following the successful completion of phase I trials, which last about one year, phase 2 trials are undertaken.

Phase 2 is split into two sub-phases; 2a and 2b. Here, the efficacy of the drug is tested on sufferers of the disease the drug is intended to treat.

Phase 2a conducts further tests on limited group of patients (less than 300). The goal is to show Proof of Concept (POC), or the demonstration of the drug efficacy. Phase 2a studies are conducted in comparison with placebos or drugs already on the market. If a new drug does not show a clear therapeutic value over-and-above the current standard of care, it is unlikely to achieve approval from a regulatory authority.

Phase 2b is concerned with the identification of the optimal dosage. Altogether Phase 2 lasts on average about 2 years.

Confirmatory – phase 3

Phase 3 trials are particularly extensive, conducted on a large scale (up to 20,000 patients) and aim at establishing the potential effectiveness of the drug. This is achieved by confirming the safety, by fine tuning the dosages, and testing the effectiveness of the treatment and the sides effects. At this stage it is also particularly important to account for individual variability, a phenomena where different patients potentially present different reactions to the same drug.

Phase 3 lasts for about two to three years. Once sufficient evidence regarding safety and efficacy is collected, a new drug application is filed with the regulatory authority. Such studies are required by regulatory agencies as evidence to support the registration of the compound.

Filing and successive approval from the FDA, which takes about one year, culminates in the granting of Marketing Authorization (MA) for producing and commercializing the product on large scale. Once on the market, the drug product is still monitored to verify possible side effects and problems which might not have arisen during previous clinical tests such as rare effects or long term effects. As a consequence the approval to a drug product can be withdrawn at any time.

All together the life cycle of a drug from pre-clinical to market is on average eight years

with some variation. For example, according to Adams and Van Brantner (2003) the life cycle of some HIV drugs can last about seven years while Parkinson's disease drugs can last up to eleven years.

The success rates

The success of a drug development process is difficult to estimate despite the availability of industry statistical database (e.g. Adis R&D Insight) including more than 20 years of historical data. The main uncertainty pertains to technical risk.

From the technical point of view, scientists and researchers cannot guarantee the final results of their work in terms of safety and efficacy of the final product. This is due to the sheer rigor of the tests that need to be passed during the various phases of development and regulatory approval. Indeed, industry statistics show that for every approved drug, roughly 10,000 molecules have failed to pass through the development tests (Van Cauter 2010). Failure rates are significant at each R&D stage and made highly probable by tight regulatory constraints.

Probability to Approval

Probability to Approval (P) is the probability of successfully reaching the approval stage and is calculated based on historical data and reflects the specific characteristics of the compounds. This means that key factors such as the therapeutic area, the specific indication, such as diabetes for example, the efficacy and safety profile, the molecular type or the novelty of the mode of action, all act as variables that influence P.

Success rates are calculated based on the evidence that starting from the preclinical phase, a drug historically fails at the different R&D phases with different probabilities. In this sense people talk about a "discharge of the risk", because the further a drug moves in the R&D process, its efficacy and the safety profile tends to improve, thereby decreasing the chances of failure.

Figure 1 illustrates discharge of risk throughout the R&D process. To calculate the probability of occurrence of each possible outcome the historical performance of 1000 compounds that entered phase 1 are considered. The drug can fail in phase 1, 2, 3 or in Submission and Registration (also called New Drug Application - NDA filing). For example, of the 1000 compounds starting phase 1 it is estimated that 350 (35%) fail while the remaining 650 pass successfully to phase 2a. Of the 650 compounds that started phase 2 about 338 (33.8%) fail and

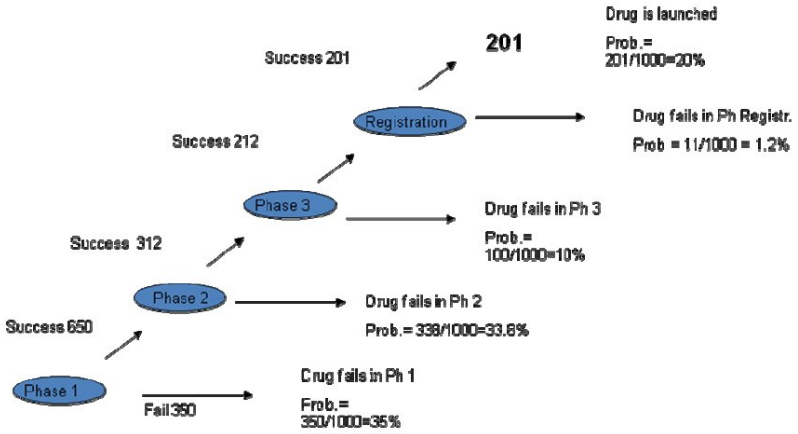


Figure 1: Discharge of Risk

the remaining 312 move successfully to phase 3. This reductive process continues so that of the 1000 that initially entered into trials, only 201 molecules are successfully launched on the market. This means that a drug in phase 1 reaches the market successfully in only 20% of the cases.

Valuation Key drivers

The method used to calculate project valuation in life science is performed by discounting the future free cash flows of a project at the appropriately weighted average cost of capital. The value of the project represents the returns generated over-and-above the cost of capital and consists of two components: the value of the explicit forecast and the Terminal Value (TV) or Residual Value.

The forecast horizon of the explicit forecast is generally 10-15 years, which captures the time taken during development and the launch phase of a new drug, up until the patent expires. After patent expiration, the sales curve drops dramatically[1] as the drug is no longer protected from generic drugs entering the market resulting in a significant loss of market share.

The Terminal Value (TV) estimates the value of a compound after patent expiry. This is generally calculated in one of two ways:

[1]The sales curve dynamic after patent expiration depends on the specific product and market, but is generally significantly decreasing.

Declining Perpetuity

This involves applying a declining perpetuity formula with a declining rate ranging between -25% to -10%. The lower limit of -25% is applied in the case of mass market products , while the upper limit of -10% is more appropriate for niche products which are subject to less generic competition.

As stated by Koller, Goedhart and Wessels (2005) the perpetuity formula assumes that after the explicit forecast period, terminating with the patent expiry date, the project earns a return equal to that of the cost of capital. The perpetuity formula is therefore calculated as:

$$TV = \frac{FCF_n(1+g)}{WACC - g},$$

where

$TV =$ Terminal Value or Residual Value

$FCF_n =$ last year explicit forecast cash flows

$WACC =$ Weighted Average Cost of Capital

g[2] $=$ expected growth (decline) rate

The formula implies that the Terminal Value (TV) is represented by the present value of a perpetual stream of a reference cash flow growing each year at a constant rate g. The reference is the cash flow during the final year of the explicit forecast period. The TV formula is only valid if g is less than $WACC$.

Explicit Calculation

The second way of calculating the terminal value is by explicitly forecasting a stream of cash flows, after patent expiry, which mimics that of a generic product.

It is interesting to note that whatever method is used, either the declining perpetuity or the explicit calculation, since the sales erosion after patent expiration covers a limited time scale of no more than 6-7 years, the amount of value represented by the Terminal Value does not account for more than 20% of the total. This reflects the highly competitive scenario after patent expiration.

[2]It can be demonstrated that in perpetuity the growth (decline) rate g is irrelevant and the project earns the cost of capital. In general since:

$$\frac{FCF}{r_e - g} = \frac{Earning(1-\rho)}{r_e - g} = \frac{Earning(1-\rho)}{r_e - \rho r_e} = \frac{Earning(1-\rho)}{r_e(1-\rho)} = \frac{Earning}{r_e},$$

where r_e is the return on equity, ρ is the plowback ratio or retention rate.

The free cash flows of a project are calculated as the cash inflows generated by product sales, less cash outflows necessary to develop, produce and market the drug. The key value drivers of cash flows are identified by :

- Sales peak and sales growth: the former represents the highest level of sales reached at the point of maximum market penetration. The growth rate determines how quickly the sales curve will rise and the consequent competitive advantage gained by the company
- Cost of goods sold: the production costs, and how these then determine the profitability of the product
- Research and development costs: to research and develop a new molecular (NM) drug is an expensive process that according to Chorchade (2006) may cost up to $Mio 800
- Marketing and selling costs: the costs sustained prior to launch, including the verification of the drug market potential and any marketing and promotional activity used to sustain the product after launch
- Cash tax: the cash outflow used for taxes which is calculated based on the statutory marginal tax rate
- Incremental working capital: the cash generated or absorbed by the business from one period to the next. The main components of working capital dynamics are represented by the monetary resources tied up in the management of account receivables, accounts payable and inventory

The key value drivers define a projects expected cash flows for each year of the explicit forecast period. The expected cash flows are then discounted at the appropriate cost of capital to obtain the project's net present value (NPV)

$$NPV = \sum_{i=0}^{n} FCF_i(1 + WACC)^{-i} + \frac{FCF_n(1+g)}{WACC - g}(1 + WACC)^{-n},$$

where:

i= year, n= years of explicit forecast, FCF_i= Free Cash Flow

$WACC$= weighted average cost of capital

$\frac{FCF_n(1+g)}{WACC-g}$= Terminal Value

$(1 + WACC)^{-n}$= discounting of the Terminal Value

As indicated by Eynon (1988) to reflect the matching principle, nominal free cash flows (including future inflation effects) are discounted at the (nominal) cost of capital.

The discount rate

The WACC represents the weighted average cost of equity and debt based on the company's debt/equity market value ratio:

$$WACC = K_d(1-t)\frac{D}{D+E} + K_e\frac{E}{D+E}$$

where

K_d= Cost of Debt, K_e= Cost of Equity, t= marginal tax rate, $\frac{D}{D+E}$ =company's target financial leverage using market values, and $\frac{E}{D+E}$ = target level of Equity to firm's market value.

The cost of capital represents the return that equity holders and bond holders earn on the basis of the company's debt/equity market value. Equity and bond holders are entitled to the returns because they bear the equity and debt risk, respectively.

In the context of project valuation, it is assumed that investors are risk averse and therefore require a higher rate of return for risky projects. The company's cost of capital should be used to discount only those projects whose risk profile is in line with the company's average risk margin.

As stated by Zingales (1998) according to the CAPM model (Capital Asset Pricing Model), the marginal investor requires compensation for the risk associated with a specific project whose outcomes are uncertain. Investors are concerned with the incremental risk of a project when added to their investment portfolio rather than the total project risk. The incremental risk is expressed as the covariance between the project returns and the market returns (r_i, r_m), the contribution in terms of risk of the single project on the market.

The ratio $(E(r_m) - r_f)\,/Var(r_m)$ equals the price per unit of risk, where r_f is the risk free rate of return, $E(r_m)$ is the expected rate of return on the market portfolio, and $E(r_m) - r_f$ represents the risk premium, or excess return in holding the market portfolio, and $Var(r_m)$ the variance of the market.

We can use the two components, price per unit of risk and the contribution to risk, to quantify the premium required by holding any asset:

$$\textit{Covariance}(r_i, r_m) \cdot (E(r_m) - r_f)/Var(r_m)$$

The ratio Covariance$(r_i, r_m)/Var(r_m)$ is the beta (β) of the asset. The premium becomes $\beta[E(r_m) - r_f]$, where the beta developed by Sharpe (1964) and Lintner (1965) represents a measure of systematic risk, or a risk that is in the "economic system" and cannot be diversified away. A project's specific risk can be diversified away and is accounted for in the cash flows forecasting by means of sensitivities .

Having defined the premium or excess return required for holding any asset, CAPM defines the expected return on any asset as $E(r) = r_f + \beta[E(r_m) - r_f]$.

The basic CAPM model (extensions such Intertemporal or Consumption Based CAPM have subsequently been developed) is well used in practice. The fundamental condition of equilibrium of the model implies that:

$$K_e = r_f + \beta[E(r_m) - r_f].$$

The cost of equity (K_e) appropriate for a specific project requires the estimation of the following main components :

- The market risk premium (MRP) is given by $E(r_m) - r_f$ and represents the excess returns over the risk free returns required by investors for bearing market systematic risk.

  There are various methods of calculating this. The most common is the "ex post" method where an estimate of the long-term arithmetic average of historical differences between the market and the risk free returns $(r_m - r_f)$ can differ depending on the sources performing the calculation. A study from Fernandez and Del Campo (2010) shows that the average MRP used by analysts in the US and Canada in 2010 is about 5.1%, similar to their colleagues in Europe (5%).

  Based on the study of Eynon (2001) considering that the valuation process is based on a forward-looking approach, while "ex post" utilizes historical data, some practitioners advocate the use of an "ex ante" estimate of MRP. With this approach, the MRP is calculated as the difference between the expected market returns and the long-term risk free rate.

- The risk free rate (r_f) is given by the expected yield on government securities over the same period as the project's lifespan matching the duration of the project. The yield curve reflects expectations about future interest rate dynamics and implies that changes in future interest rates embed risk premium. This is why practitioners deduce from the

long-term rate a percentage value for the risk premium. The risk premium is calculated for the US market by applying CAPM to estimated betas of long-term government bonds, that is Risk premium = beta · MRP.

- The project beta measures the level of covariance of a project's cash flows with the market portfolio. It can be approximated by the company's or sector beta if the project replicates the company's business level of risk. In life sciences, the beta[3] is smaller than 1 meaning that the industry is less risky than the market as a well diversified portfolio and implying a lower return for the investors. The beta is commonly calculated by regressing the company's monthly returns against market returns over a period of 5-10 years. One issue that can occur is that the beta (and therefore the cost of equity) of the entire company may not be appropriate for the specific part of the business in which the firm operates. For example, within a pharmaceutical conglomerate business, units like OTC products or animal drugs have distinct risk characteristics from the pharmaceutical development. In this case a peer group analysis can be applied to provide separate estimates of the beta for each business.

  The peer group analysis aims at identifying comparable twin companies such as firms in the same line of business or firms sharing the same risk characteristics in term of operating leverage. The beta calculated from a firm's peers will need to be unlevered and then relevered to reflect the capital structure (financial leverage) of the business unit for which the beta is being estimated.

  Taking the simplifying assumption that the beta of debt for a given company is zero (based on the assumption that claims prioritize debts first and debt is essentially risk free) the following relation holds:

$$\beta_l = \beta_u(1 + (1 - t)D/E)$$

  where

  β_l= beta of the company reflecting the capital structure (financial leverage)

  β_u= beta unlevered from the capital structure therefore reflecting only the operating leverage

[3]Golec and Vernon (2007) calculated market beta for pharmaceuticals using 1982-2005 data. The authors found an average value of about 0.92. Harrington and Miller (2009) calculations using 2001-2005 data show a smaller value of about 0.69.

t= marginal tax rate

D/E= market value of debt over market value of equity, that is the company's financial structure

The intuition behind the relation stated above is that the company's β is affected by the operating leverage and the financial leverage. The higher the fixed cost, the higher the variability of the operating income and therefore, other things being equal, the higher is the β. In the same way an increase of financial leverage, other things being equal, determines an increase of the β.

Once the beta, the MRP and r_f are known, the cost of equity, (K_e), that is the expected required return for shareholders can be calculated by applying the CAPM.

The second component used to estimate the WACC calculation is the cost of debt (K_d).

Since interest expenses are tax-deductible, the required return on debt is the after-tax cost of debt. A project's incremental cash flows need to be discounted by a rate that reflects the incremental cost of debt, since what matters is the incremental opportunity costs. The cost of debt is generally derived by considering the company's specific rating which determines the cost of debt. Alternatively, this can be achieved by looking at comparable peers in the same line of business with similarity in terms of operating and financial leverage. Comparable companies' long-term bonds yield to maturity can thus be used to estimate K_d.

Limitations of CAPM

According to Zingales (1998) there are some caveats referring to the main assumptions underlying CAPM that needs to be taken into accounts when applying the model.

- Investors use portfolio theory, prioritizing concerns over the mean and variance of their end of period wealth.

- The marginal investor holds a well diversified portfolio of assets, therefore diversifying away a company's specific risk.

  When the second assumption is violated, investors are entitled to be compensated not only for systematic risk, but also for that part of specific risk that is not diversified.

eNPV versus NPV: an application of success rates

Success rates are employed to calculate the expected Net Present Value (eNPV) of a project according to the phase within which it is located. Because investment decisions in R&D face a multitude of uncertain outcomes, simple NPV which estimates only one possible distribution outcome, (that is the drug will not fail any of the development stages and will be successfully launched) is unrealistic. In this way technical risk, that is the risk of all possible outcomes, is ignored. In the pharmaceutical industry there is a distinction between NPV and eNPV. NPV is used under the unusual assumption that a drug is successfully developed and launched. The eNPV extends the NPV by accounting explicitly through probabilities for the uncertainty related to development and launch.

For a more accurate estimate of an investment value we need to consider all outcomes. Expected NPV (eNPV) calculates the weighted average of the probability of occurrence of the NPV for each possible outcome.

The difference between NPV and eNPV can be significant especially for early development molecules where a high negative eNPV has reasonable likelihood of occurrence.

The eNPV can be seen as a rough approximation of Real Option (RO) valuation and Decision Trees (DT). What eNPV does implicitly, RO and DT do it explicitly. As the project progresses, more information becomes available and managers are able to react and delay, abandon or scale up investment according to new information made available in the development process. Real options and Decision Trees try to capture this flexibility. The eNPV is able to capture outcomes only related to technical feasibility, but fails to incorporate all outcomes that have reasonable probability of occurrence but are not associated with technical risk, such as the option to scale up projects and compound options more generally.

Calculating Probability to Approval (P) and probability of cash flows

Based on historical performance of compounds in the Pharma R&D process, researchers are able to estimate the probability of success through each phase. The probability of success or failure at each phase is described by the Bernoulli random variable X with probability p and $1-p$, where the Bernoulli function $f(K,p)$ is defined as follows:

$$f(K,p) = \begin{cases} p & K = 1 \\ 1-p & K = 0 \end{cases}$$

	Pre-Clin.	Ph I	Ph II	Ph III	Reg	Approval
	6%	20%	31%	65%	95%	
Prob.of moving to the next phase	30%	65%	48%	68%	95%	
PoSpending PC	100%	30%	20%	9%	6%	
PoSpending Ph I		100%	65%	31%	21%	20%
PoSpending Ph II			100%	48%	33%	31%
PoSpending Ph III				100%	68%	65%
PoSpending Reg					100%	95%

Figure 2: Probability to Approval (P) and probability of cash flows

$p = E(X)$, reflects the number of compounds in each phase passing successfully to the next one.

$p = E(X)$ is given by n_s/n, where

$n = n_s + n_f$, n_s= number of success, and n_f= number of failure

This probability of success is specific for each Therapeutic Area (TA), indication, type of molecule, such as biologic vs. small molecule (SM), and compound, either New Molecule (NM) or Life Cycle Management (LCM). For example, when considering the asthma indication in the Respiratory Therapeutic Area (TA), a SM and a NM compound will have specific probabilities to move ahead in the development process from preclinical phase to registration. In general antibiotics are more likely to be successful, because they present a mode of action easily testable outside humans. In the same way premiums are recognized to biologics since they represent targeted more predictable therapies. LCM drugs have more chances of success since they can leverage on other compounds that have already been shown working in another indication.

Figure 2 refers to a specific Therapeutic Area (TA), indication, Small Molecule type and New Molecule compound. We see that the probability of moving successfully from the pre-clinical phase to phase 1 is about 30%, from phase 1 to phase 2 is 65% and so forth. This data informs calculations on the probability of final approval and subsequent access to market. The probability of a compound in phase 1 reaching the market is calculated by the product of the probability's at each phase, from phase 1 to approval. The probability of a compound in phase 1 reaching the market is therefore 20% given by the product of 65%·48%·68%·95%. The probability of a compound in phase 3 reaching the market would therefore be 65% (68%·95%). However, the probabilities of each phase are conditional probabilities, dependent on the assumption that all previous phases were successful.

Once we know the probability of a compound passing through each phase we can also calculate the probability of cash flows (or probability of spending). For example, clearly the project is "alive" during phase 1, therefore the probability of spending, i.e. the probability to be applied to cash flows is 100%. In phase 2 the project is still alive if the project successfully passed phase 1, under these conditions the probability of cash flow is calculated as 65%. This is calculated as the product of 100% representing the chances of the project being in phase 1, times 65% representing the probability of successfully moving to phase 2 (see figure 2). These probabilities applied to cash flows remain constant throughout the duration of the specific phase, therefore, cash flows of phase 2, which last about two years, are probabilised for two years at a rate of 65%. Cash flows of phase 3 lasting for about two years are probabilised at a rate of 31%[4]. This allows researchers to obtain expected or risk adjusted cash flows, employed in the calculations of eNPV. From year seven onwards, after the approval phase, the cash flows are probabilized at a constant 20%, which is ultimately the probability of entering into the market for a drug in phase 1.

Calculating eNPV

We can see an example in detail (figure 3 – eNPV calculation) where we calculate the eNPV value in a "simplified way", by just applying the probability of spending (or probability of cash flows) to each cash flow. This is possible when there are no embedded options and the structure of the development phases reflects a simple binomial tree. Each year cash flow can be directly multiplied by the probability of cash flows to calculate the eNPV. In other words instead of assigning probability to each outcome, we assign probabilities to yearly cash flows.

We have seen before how probabilities of cash flows are calculated, (see figure 2) and applied to the yearly cash flows according to the duration of each phase. The next step is to discount the probabilised cash flows to obtain the eNPV, as in the example in figure 3 below:

Figure 3 shows that the eNPV is only $Mio 33 against a simple NPV of $Mio 668 USD. As previously mentioned, a valuation using NPV assumes that the drug will not fail any of the development stages and will be successfully launched. The NPV assumption is that the drug is successfully developed and launched, while the eNPV accounts explicitly for the uncertainty related to development and launch through probabilities. In ignoring risk factors that may cause a drug to fail at any stage, simple NPV is overly optimistic.

[4]The value of 31% is obtained by multiplying 65% representing the chances of a project being in phase 2, times 48% representing the probability of successfully moving to phase 3.

	Year 2010	Year 2011	Year 2012	Year 2013	Year 2014	Year 2015	Year 2016	Year 2017	Year 2018	Year 2019	Year 2020	Year 2021	Year 2022	Year 2023	Year 2024	Year 2025
	Phase 1	Phase 2	Phase 2	Phase 3	Phase 3	Regist.	launch	Market	Market	Market	Market	Market	Market	Market	Market	Market
Net Sales							63	111	147	187	231	280	306	333	327	317
Cogs @8%							-5	-9	-12	-15	-18	-22	-24	-27	-26	-25
R&D	-2	-4	-4	-10	-10	-11	-7	-2								
Marketing						-42	-83	-41	-54	-69	-85	-103	-113	-123	-121	-117
G&A							-2	-3	-4	-6	-7	-8	-9	-10	-10	-10
Operating Profit	-2	-4	-4	-10	-10	-53	-33	56	76	97	120	145	159	173	170	165
Income Tax @30%	1	1	1	3	3	16	10	-17	-23	-29	-36	-44	-48	-52	-51	-49
Net Income	-2	-3	-3	-7	-7	-37	-23	39	54	68	84	102	111	121	119	115
Working Capital							13	22	29	37	46	56	61	67	65	63
Delta Working Capital							13	9	7	8	9	10	5	5	-1	-2
Cash Flows	-2	-3	-3	-7	-7	-37	-36	30	46	60	75	92	106	116	120	117
Present Value @ 10%	-2	-3	-3	-5	-5	-23	-20	15	22	25	29	32	34	34	32	28
Cumulative PV	-2	-5	-8	-14	-22	-59	-95	-65	-19	41	117	209	315	431	551	668
Probability of spending	100%	65%	65%	31%	31%	21%	20%	20%	20%	20%	20%	20%	20%	20%	20%	20%
Probabilized Cash Flows	-2	-2	-2	-2	-2	-8	-7	6	9	12	15	18	21	23	24	23
Present Value @ 10%	-2	-2	-2	-2	-2	-5	-4	3	4	5	6	6	7	7	6	6
Cumulative PV	-2	-3	-5	-7	-8	-13	-17	-14	-10	-5	1	8	14	21	27	33

NPV @ 10%	668
eNPV @ 10%	33

Figure 3: eNPV calculation

We applied the probabilities of cash flow based on the average time a compound remains in each phase. This information is drawn from empirical studies covering previous R&D projects in the Pharma industry. Like probabilities of success, cycle times for each phase are also influenced by the Therapeutic Area (TA) and indication of the compound. In general we can say that phase 1 lasts about one year, phase 2 (including phase 2a and 2b) lasts about two years, phase 3 is in general the longest and most expensive phase, lasting about two to three years, while the registration phase lasts about one year.

We have seen how to calculate the eNPV in a simplified way, by assigning probabilities to each years' cash flow. Another way to calculate the eNPV is to assign probabilities to all the possible outcomes. Referring to figure 1, based on historical performance of about 1000 molecules passing through each development phase, we can assume the following conditional probability of occurrence of each outcome, leading to a probability of success of 20%:

- A drug fails in Phase 1 with probability of 35%
- A drug fails in Phase 2 with probability of 33.8%
- A drug fails in Phase 3 with probability of 10%
- A drug fails in Phase Registration with probability of 1.2%

The NPV of each outcome is first calculated based on the cash flows forecasted at each stage of the development process. In this way, considering the previous numerical example, the outcome "drug failure in phase 3", for example, has a negative NPV of -16.9. As we can see from figure 4, this is the sum of the cash flow NPVs from preclinical trials to phase 3, when the drug fails: -16.9 = -1.6-2.8-2.5-5.1-4.9. Therefore, $Mio 16.9 represents the NPV of all costs sustained by Ph3, when it will fail and thus drop out of the R&D Pipeline. Notice that the value of $Mio 190.4, corresponding to the outcome "drug is successfully launched", includes the NPV of the stream of cash flows ($Mio 230.4) of the product successfully launched on the market.

To calculate the eNPV we consider the probability of occurrence and NPV of each outcome. For example (figure 5) the outcome "drug fails in phase 3" has an NPV of -16.9 which is multiplied by the probability of occurrence of that event, 10%, leading to a eNPV of -1.7. The total eNPV is the weighted average of all possible outcome weighted by their probability of occurrence. The final result eNPV of 33 is the same that was found before by directly

CASH FLOWS $Mio	2010	2011	2012	2013	2014	2015	2016-2026
	Phase 1	Phase 2	Phase 2	Phase 3	Phase 3	Registration	launch
sales							
COGs							
marketing costs						-42.0	
development costs	-2.3	-4.3	-4.3	-9.7	-10.3	-11.0	
taxes @30%	0.7	1.3	1.3	2.9	3.1	15.9	
Cash Flows	-1.6	-3.0	-3.0	-6.8	-7.2	-37.1	
Present value of cash flows @10%	-1.6	-2.8	-2.5	-5.1	-4.9	-23.0	230.4

POSSIBLE OUTCOME	NPV						
Drug failure in Ph1	-1.6	-1.6					
Drug failure in Ph2	-6.9	-1.6	-2.8	-2.5			
Drug failure in Ph3	-16.9	-1.6	-2.8	-2.5	-5.1	-4.9	
Drug failure in Registration	-40.0	-1.6	-2.8	-2.5	-5.1	-4.9	-23.0
Drug is successfully launched	190.4	-1.6	-2.8	-2.5	-5.1	-4.9	-23.0 230.4

Figure 4: Outcomes' NPVs

POSSIBLE OUTCOME	PROBABILITY	OUTCOME eNPV
Drug failure in Ph1	35.0%	-0.6
Drug failure in Ph2	33.8%	-2.3
Drug failure in Ph3	10.0%	-1.7
Drug failure in Registration	1.2%	-0.5
Drug is successfully launched	20.0%	38.1
eNPV		33.0

Figure 5: Outcomes and eNPV calculation

probabilizing the cash flows without having to calculate the NPV of every outcome. This is possible when decisions within the development process are represented by a binomial structure in terms of go or no-go decision. Nevertheless when the structure becomes more complex, implying the existence of a compound option, then the shortcut of applying probabilities directly to the cash flows is not applicable and each outcome NPV needs to be identified. One example is represented by the possibility of out-licensing a compound. This often occurs when the results of the certain phase are not as promising or strategically interesting, and the company may decide to pursue outside opportunities by out-licensing the compound to another company, creating a compound option.

The eNPV calculation shows a more accurate valuation of each project in the R&D pipeline than the NPV. A positive eNPV is an indicator that the opportunity is worth pursuing, but there

are two further aspects that need consideration: diversification and expectation.

Diversification

The probabilities of success represent estimations about the success of an R&D program. In big pharmaceutical companies the risk of an unsuccessful R&D program is mitigated by the diversification effect. This means that large companies' pipeline is made up of many projects that reduce the risk exposure. Such exposure however is maximized in small biotech companies whose success depends on very few molecules.

According to Grossmann (2003) the degree of diversification allows the reduction of a company's idiosyncratic risk. This applies only to the company, not to te shareholders that have bigger possibilities of diversification. Some risk however still exists within the standard deviation around the average probabilities of success, since a perfect diversification is not possible. As an example of firm-specific risk we could consider a molecule-specific risk related to the chemical structure that can show various levels of safety and efficacy in its application. In a portfolio pipeline made of many molecules, the chances of finding a chemical structure with an adequate level of safety and efficacy are high but never reach certainty. A business that does not diversify is exposed to potential dangers. Typically in the pharmaceutical industry a diversification strategy is pursued to decrease managerial risk . A higher level of diversification reduces the business risk related to the failure of molecules in the pipeline.

Expectation

The second consideration to make is that a projected eNPV calculated based on probabilities of success represents an expectation or an average value of the compound on the long run. The concept of expectation implies that the trials success or failure will be executed many times. We do not know if the compound will be successful or if it will fail, in which case it drops from the R&D pipeline and its value gets to 0. We only know that on average, based on historical performance data, the molecule will have a certain likelihood of success in reaching market launch. This idea of an infinite series of "repetitions" standing behind eNPV is often ignored leading to decisions that are taken at the firm level based on eNPV, without considering that in reality there is only one repetition that can lead either to a successful or a failing molecule. This information on the probability of occurrence is not accomplished by simple scenario analysis.

The use of sensitivities

It is common practice in the industry to support the valuation with sensitivities around the base case results.

Sensitivities around the base case results are limited to finding an optimistic case and a pessimistic case to give the decision manager the sense of the "cash in cash out" dynamic involved in these two extreme scenarios. The sensitivity is made around the key forecast parameters including sales forecast, marketing expenses and development costs. Sales forecasts are the main value driver and are based on epidemiological studies to define patient targets. Patients targets multiplied by the market share give the relevant number of patients. Sales forecasts are thus obtained by considering the relevant number of patients, the assumed daily dosage and the dose price.

Many Health Authorities recognize a price premium only to certain drugs, so when negotiating a price for a drug, certain factors must be considered in order to get the highest premium. It is crucial that there is clear differentiation from competitors in term of safety, efficacy and convenience (the way the drug is administered to patients). Another key factor is the evolution of the sales curve and at what point peak sales are estimated to be achieved. Peak sales reflect the highest level of sales reached in the market and represents the level of maximum penetration. If the sales curve uptake is fast the company will benefit from a first mover advantage towards competitors, and a bigger share of value will be generated in the first year of the drug's life.

The sensitivity around the base case scenario does not cover the risk and uncertainty behind the decision making process in R&D. If we consider risk as the probability of a discrete event[5] occurring and the variability, or standard deviation, in possible outcomes of each scenario, we see all the limitations of the optimistic-pessimistic case approach. These can be summarized as:

- This approach does not consider any variability around the technical risk (P is not simulated).
- The approach does not cover all the risks and uncertainties of market environment. In particular we have to consider that sales explicit forecasts cover about 10-15 years post-launch. During this time frame the competitive position is constantly changing.

[5]Event is a subset of the sample space Ω and can comprise one or more possible outcomes ω (Stirzaker 1999).

- Decisions in the development phase need to be taken many years before the compound will be commercialized on the market.

Based on the work of Ekelund (2005) a range of various approaches can be used to gain a perspective on risk and uncertainty. At one end of the scale there is the simple base case probabilized scenario, at the other end we have the most informative and complex real option approach. In between there is the discrete multi scenarios approach, decision trees and numerical techniques, like Monte Carlo.

As the future is uncertain, all possible alternative scenarios must be considered, in which each of the key parameters representing market or technical risk can differ. Market risk reflects changes in sales trends, marketing and development costs, date of launch, market uptake or competitors dynamic. Technical risk deals with the probability of success through the development process. Although it is practically impossible to consider and quantify all the variables, it is important is to recognize when the analysis in the valuation process is oversimplifying reality.

It is possible to identify four main situations defined by various levels of market and technical risk.

1. When the uncertainty around the market is low, for example when the compound is an LCM and the R&D process does not present large uncertainties, then traditional valuation techniques, like eNPV, can be utilized.

2. If the market potential is sure but the R&D results are uncertain, then the valuation is best supported by tree diagrams and decision analysis. Decision Trees in these cases allow to capture the flexibility required to cope with uncertain technical results.

3. In cases where the market uncertainty is high, for example because the molecule has multiple indications while the R&D process is easily predictable, Monte Carlo simulations would be the most appropriate technique to be used.

4. When the complexity is maximum and high market risk is coupled with high technical risk a real option analysis becomes the most appropriate approach. In such complex scenarios, RO is the appropriate tool to capture not only management strategic flexibility decisions, but also the change in discount rate required to reflect the change in the project riskiness.

Decision Trees

The uncertainty of outcomes surrounding R&D phases has strategic implications that are scrutinized within a formal decision analysis context. Senior management within a pharmaceutical company typically sets the strategy of the portfolio and make decisions motivated by the need to prioritize projects that could change the standard of care and gain a first mover advantage over competitors. Decisions such as how many indications to develop within the portfolio or which indications target current unmet medical needs for example, are carefully analyzed as they contribute to the identification of an optimal strategy. The goal of the optimal strategy is to lead to the highest eNPV.

Decision trees help to structure such analysis where the main strategic elements are made available in a graphical form to the decision maker. The tree displays, in chronological order, all possible strategies. Each strategy is viewed as part of a sequence of future choices, and their implications are viewed in term of outcomes and the likelihood of such outcomes occurring over a given timeframe. Such decision trees are thus structured as a multi-period decision process.

Gathering information on outcome probabilities is problematic as such data is reliant on the "subjective" probabilities expressed by managers and experts in the field. In life science decision problems it is rare to be able to obtain outcomes probabilities on the basis of historical data. This is because each project tends to be so specific that the performance of previous projects can be of little or no help in forecasting a current project's future events.

The decision tree also displays the monetary payoff following each strategic decision. Once all these details are available and formally structured within the framework of the decision tree, managers can more easily identify an optimal strategy to implement. There are various decision criteria that can be used but the most common is the Expected Monetary Value (EMV). This is the highest expected profit or, more frequently, the highest expected NPV generated by the initiative.

According to Albright, Winston and Zappe (2009) the EMV of each strategy is a weighted average of all possible related outcomes, weighted by their probability of occurrence. Taking expected values it's like playing averages over a set of results assuming that we can replicate the "game" an infinite amount of times . The long run EMV is a best fit and will never reflect the 'true' value for the firm that results from a decision. According to Goodwin and Wright (2009) this is particularly relevant where a given decision is not replicable, such as one-off

decisions when large monetary values are involved. Under these circumstances if the strategy adopted turns out to be wrong, consequential losses will not be recoverable by repeating the choice over time.

As well as replicability issues, EMV criteria do not take into account the decision maker's incidental effects. According to Keeney (1982) for example, a technical operations manager may be willing to reject a project (despite its average value creation) due to potential negative consequences outweighing the positive, such as a decrease in market demand in terms of a plant's capacity utilization, for example. This risk concerning the demand dynamic may, however, be acceptable to a marketing manager. Therefore, the two managers present different attitudes to risk that are not adequately represented by EMV. To account for the differing attitudes to risk, as stated in Dixit, Skeath and Reiley (2009), monetary payoff results must be translated at different levels of utility. In this translation process, the monetary value payoffs are converted using a non-linear rescaling function, or utility function. In the context of rational choice, decision makers will take decisions that maximize their expected utility by following the principle of expected utility maximization in uncertain situations as defined by Von Neumann and Morgenstern (1947).

Although representing a well diversified shareholder, the EMV fails to capture the fact that managers are not well diversified. This because a big percentage of human capital is employed in the company.

This technique remains the most applied methodology in business practice. Despite its limitations, EMV can be justified in two ways: first, each project is part of a diversified portfolio where the monetary implications of various decisions tend to even out over time. Second, it is practically impossible to define a company's utility function by reflecting each manager's individual attitude to risk.

Decision trees as explained by Vose (2008) are useful to decision makers to understand the logic of a problem, its risk profile and communicating it effectively.

A decision tree can be illustrated using applications relative to the strategic development and positioning of a compound. The goal is to assess the therapeutic potential of a drug, and maximize its commercial value by selecting the most appropriate strategy.

Traditionally, pharmaceutical companies try to increase the rate of success and maximize the value of a compound by targeting additional indications. This is part of life-cycle management, where the same compound is developed for additional indications[6] resulting in new

[6]In life science a new indication of an existing drug refers to the application of the drug to treat a different

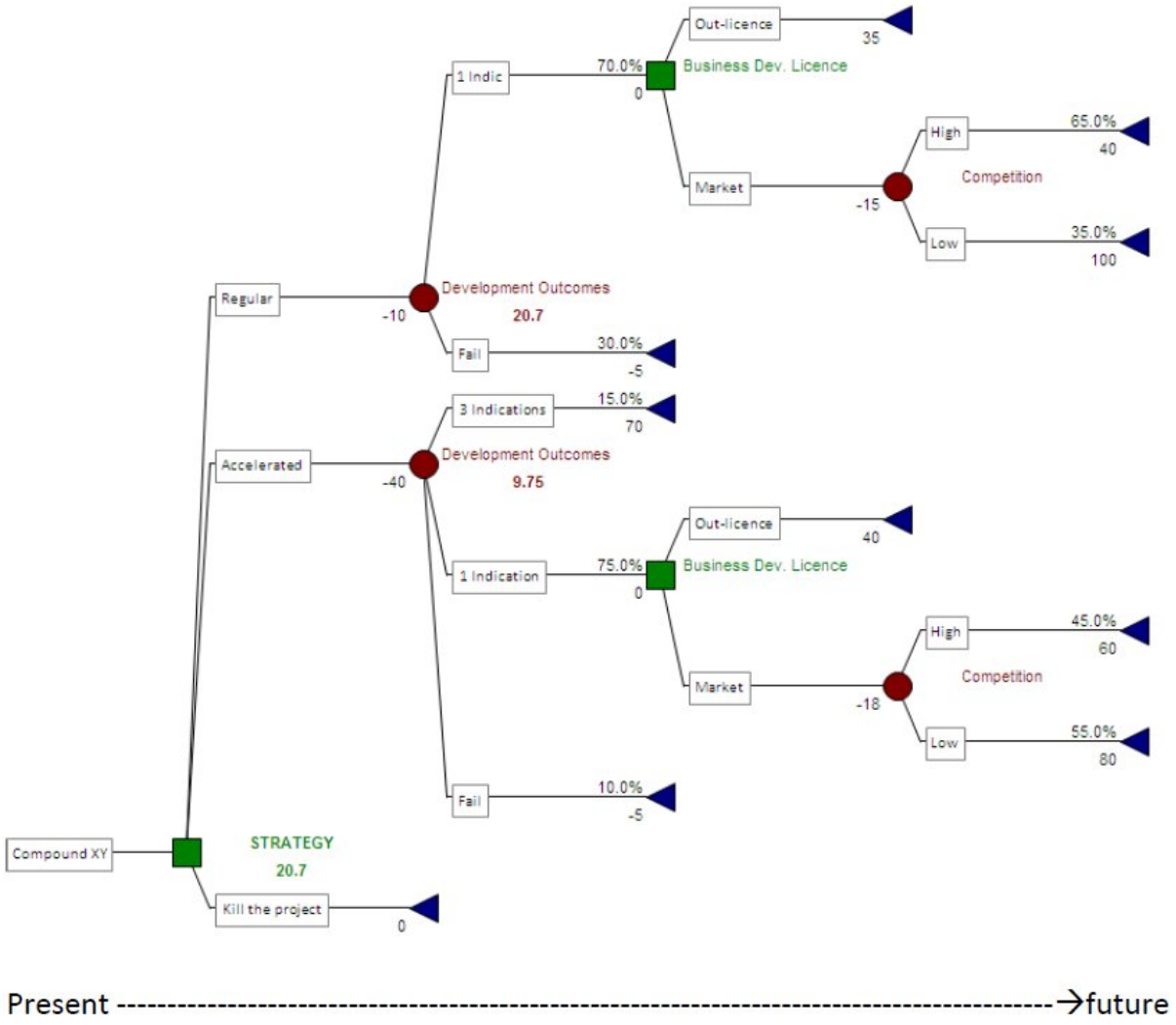


Figure 6: Decision tree for compound XY in phase 3 of development

drugs and reducing development risk. The probabilities of success are increased by the availability of safety and efficacy data.

For illustrative purposes a compound XY which has successfully passed phase 3 is considered. Figure 6 outlines the various strategies pertaining to its future development, which still need to be determined. Based on Clemen and Reilly (2001) each decision point is represented by a square, generating branches that represent an alternative course of action. While each decision point is under the control of the management, subsequent alternative courses of action can generate consequences that are not under the managers' control. These are uncertain events graphically represented by a circle. The possible outcomes generated by uncertain

disease.

events each have a specific probability of occurrence. These branches represent a set of mutually exclusive and collective exhaustive outcomes. Decision points and uncertain events are sequentially combined over time leading to an overall route strategy. Each route estimates the expected monetary payoff, in terms of NPV, applied by the decision maker to choose the best course of action.

In figure 6, compound XY can be developed following three different routes, so the decision maker is facing a decision point from which three strategic branches are developing.

1. Regular

   The Regular strategy reflects the development plan currently in place based on the status of other Regular projects within the company's portfolio. This option implies that the drug will be developed at a standard pace and the development costs will amount to around $10Mio.

2. Focus on acceleration

   This option assumes increasing the speed of development activities, and reducing the time to launch in order to gain a greater competitive advantage. The accelerated development costs are estimated at about $40Mio.

3. Kill the project

   A final alternative involves terminating the project with a consequent saving of development costs.

The outcomes following each strategy are uncertain and outside the control of management: a project may be successful leading to the development of multiple indications, or it might fail. In the case of the regular strategy, given the recent study results the management is confident that at least one indication could successfully be launched on the market with a probability of 70%. If an accelerated strategy is pursued, the probability of reaching a successful indication is slightly increased, together with the possibility of reaching multiple indications. The accelerated strategy implies a probability of 15% to develop three indications, a probability of 75% to develop one indication and a 10% probability of failure.

In the case of successful development of one indication, a business development decision is required. Here, the options are either to out-license the compound to an external partner or to launch it independently onto the market. The positive cash inflow from a license deal is

estimated at about $35Mio, while the marketing costs connected to the launch of the product would be about $15Mio in the case of the regular strategy.

The accelerated strategy implies cash inflows from a license deal of about $40Mio and marketing costs of $18Mio.

The dynamics of market demand are uncertain and can lead to higher or lower NPVs depending on the competitive situation. In figure 6, the probability of facing high competition is 65% with a project NPV generation of $40Mio in the regular strategy, compared with a probability of intense competition at 45% and a positive NPV of $60Mio for the accelerated strategy. Conversely the probability of facing a low competitive situation would be 35% and 55%, following a regular strategy or an accelerated one respectively. The corresponding NPVs are estimated as $100Mio in case of regular strategy and $80Mio in case of an accelerated strategy.

Rolling back

The process used to identify a strategic decision with the highest EMV, is called rolling backward. As illustrated by Hespos and Strassmann (1965), this process begins with the final payoff value, and then works back through the decision tree reflecting how current business choices are strategically connected with future planned choices. The decisions we take today can open or close future opportunities.

At each uncertain event the expected value is calculated so that at each decision point the route resulting in the highest EMV is selected. In this way sub optimal branches, those reflecting lower EMV, are progressively pruned leaving only the optimal alternative.

We can see from the example how the tree is rolled back to determine the best alternative strategy:

At each chance node, the expected NPV value is obtained:

$$\sum_{\substack{0\leq i\leq m \\ 0<j<n}} P_{i,j} \cdot NPV_{i,j}$$

where

$P_{i,j}$ is the probability connected with the chance node i, j.

At each decision point the alternative with the highest NPV is selected according to:

$$\max(NPV_{i,j}up, NPV_{i,j}down)$$

In the case of figure 6, the best strategy selected is the regular strategy as this creates a value of about $20.7Mio, compared with $9.8Mio of the accelerated strategy and $0Mio of the Kill the project strategy.

The value of the regular strategy is created from the end node on the far right of tree, the competitive chance node.

Given the NPVs estimations outlined before, the competitive situation leads to an expected value of (40·65%+100·35%)=$61Mio. The net value, after deducting the marketing expenses ($15Mio) required for launching the product, is $46Mio.

At the Business Development License decision point of the regular strategy, the Market strategy is preferred to the Out-license strategy (value created is $46Mio versus $35Mio, mainly generated from upfront, milestones and royalty streams from the out-license deal). Moving back through the tree towards the present, the expected value of the development uncertain event is calculated as (46)·70%+(-5)·30%= $30.7Mio, where -5 represents the development cost incurred but not recoverable due to the program failure. The net value of the Strategy, $20.7Mio is therefore achieved by deducting the $10Mio required to develop the compound from the expected value of development uncertainty. Essentially the net value of the chosen strategy is determined by expected revenues and costs of unknown events over which management have no control and estimated revenues and costs of known events over which they do have controls.

Monte Carlo simulation

The Monte Carlo (MC) method is applied in life science to analyze various uncertainties that can occur both in the development of a drug, and when calculating its potential market value. The latter application is concerned with the dynamics of those uncertainties that lie behind the commercial and marketing strategies of any one particular drug. In essence, as described by Cherubini and Della Lunga (2001) the Monte Carlo method works by recreating a synthetic random simulation, running it multiple times under various conditions and storing the results. Thus the analysis of uncertainties is achieved via the application of an artificial model.

As described by Rubinstain and Kroese (2008), the simulation uses pseudo random numbers produced by computer based algorithms, to produce sequences of independent uniform

random variables. Probability theory is used to generate further random variants from other specific distributions.

They are referred to as pseudo random numbers to acknowledge that while they 'appear' random, they are in fact computer generated using a deterministic formulae. They are therefore not truly random but repeat themselves after a certain period.

A true sequence of random variables $U_1, \ldots, U_n$ presents two main characteristics: U_i is distributed uniformly on $(0, 1)$ and the U_i are independent. The two aspects are important as they imply that U_i are uncorrelated and do not show any pattern being unpredictable from other elements of the sequence.

Various methods have been developed to recreate randomness, given the importance of the random (pseudo) numbers in driving the Monte Carlo simulation, where the numbers sequence might invalidate the simulation. The random sequences are, in fact, used to generate representative samples from the probability distribution being simulated. Good references concerning the Monte Carlo method are Jackel (2003) and Glasserman (2000).

Uncertainty and risk evaluation

The Monte Carlo technique is a powerful valuation tool for developing strategic plans that support the decision making process. It can be used to estimate a drug's potential market value while gaining a better understanding of the dynamics of those uncertainties surrounding a drug's value. This information is crucial when defining a marketing strategy shaped by the risk profile of the project.

With the application of MC we quantify a given project's risk by performing uncertainty analysis. Uncertainty is defined as an "objective feature of the universe" while risk as the "subjective measure of how one feels about the various possible outcomes of an uncertain event" (Savage 2003).

There are numerous factors of uncertainty that have an influence on a project's value, and the complexity and the dynamic interactions of these factors cannot be properly analyzed by deterministic models. For example, performing a valuation based on expected cash flows (like NPV or eNPV) assumes that there is no flexibility to deal with changes in key market value drivers such as sales growth, market share or pricing dynamics. In reality, a project's cash flow, calculated over a time horizon up to patent expiry, is more volatile because intervening variables such as demand, pricing levels and competition can change dramatically over time.

A further drawback of deterministic models as noted in Rees (2009) is that they lead to a single point output. A single point estimate, i.e. a single value output is of little use when taking decision. What is more relevant is the shape of the distribution of values, the range of outcome values the drug can assume and their individual probabilities of occurrence. According to Mun (2004) in the context of fair risk comparison between projects and consequent financial feasibility, it is important to be able to answer questions that reveal which outcomes and outcome probabilities make a project's value vulnerable; either by reaching an unacceptable threshold value, or by being negative.

A further criticism of deterministic models using best guesses (averages) of uncertain inputs as single point estimates is that this can cause misleading results, known as the flaw of averages as defined by Savage (2009). In putting average values (best guesses) as inputs in functions of random variables result in the correct average output only in certain cases such as with linear function; where average inputs generate average outputs. In other circumstances, when functions are not linear, submitting average inputs into the model will lead to a flawed average output.

This is explained by Jensen's inequality (1906), that states the following:

$F[E(X)] = E[F(X)]$ only when the function of random variables is linear. When the function is not linear the following inequalities hold:

$F[E(X)] > E[F(X)]$ when the function is concave, the functional formula evaluated at the average input is bigger than the average value of the formula.

$F[E(X)] < E[F(X)]$ when the function is convex, the functional formula evaluated at the average input is smaller than the average value of the formula.

Only in the simplest valuation models are random variables linear combinations, the majority of cases deal with non linear relationships. In these cases only by running an MC simulation can we estimate the true average of the uncertain output value. Thus only a stochastic cash flow model leads to a distribution of a projects value and risk, and using such models each drug project is therefore valued by both its return and its risk profile.

The quantification of the project risk triggers additional steps toward the application of real options. Strategic thinking in terms of real options involves first acknowledging the risk, valuing it and finally hedging it. Ultimately considering strategic options like expansion, contraction, abandonment or switch is a way of positioning and taking advantage of risk.

Chapter 1

Real options in the pharmaceutical industry

1.1 The limitations of the DCF method

For years practitioners and academics have argued over traditional Discounted Cash Flow (DCF), with many claiming that this method does not capture the options embedded in most corporate decisions.

This oversight regarding the strategic value and flexibility of active management has resulted in a discrepancy between the calculated value using traditional DCF (leading to Net Present Value NPV, or some other variant) and the "true" value.

In particular, there are factors which are not adequately accounted for in the traditional DCF approach (Dixit and Pindyck 1994). These will next be discussed.

1. Uncertainty can derive from two main sources: external or systematic risk (such as market risk) and internal or specific risk (such as organizational or technological company specific risk). The traditional capital budgeting approach recognizes the risk of future cash flows. It discounts those flows at a project (or company) specific discount rate that reflects the perceived risk so that uncertainty is measured only indirectly. This occurs because the discount rate represents the opportunity cost of capital, or the rate of return, that investors expect from investments that share the same risk profile.

2. The DCF approach assumes that cash flows follow a rigid path that ignores flexibility to fluctuations in the exogenous and endogenous conditions. This leads to further uncer-

tainty over the traditional approach in terms of flexibility and the possibility of optimizing the timing of the investment decision. Traditional DCF fails to consider the value of active management necessary to mitigate risk and preserve value. The NPV rule tends to be a "now or never" approach that compares the value of taking an action now (investing), against the value of never taking that action (not investing). It therefore replaces future flexibility with a predetermined commitment that incorporates the economic (cash flow) consequences of that decision set at a specific point in time.

3. Traditional DCF analysis fails to recognize irreversibility as a cost. In reality, most investments costs are irreversible since there is an opportunity cost of investing in the specific project and a cost of committing resources in an irreversible way. Therefore such investments are only justified if their returns are adequate. An investment made today under uncertain payoff conditions requires a premium to compensate for lost flexibility (McDonald and Siegel 1986). The analogy between irreversible investment opportunity costs and call options is outlined by Dixit and Pindyck (1994); once exercised both present the characteristic of irreversibility and their value takes into consideration the uncertainty of future outcomes.

The above limitations of traditional DCF highlight the challenge of finding a way of capturing some of the value lost by the DCF approach, thus justifying investments in negative NPV projects. For example, in the pharmaceutical business early stage projects in the preclinical phase with negative expected Net Present Value (eNPV) can be continued despite their (apparent) value destruction because they represent strategic investments in R&D that generate flexibility. The correct way to interpret this is to consider that the preliminary R&D investment knowledge and information is gathered, that allows a company able to respond in a flexible way to future events. This ability to learn and respond (Shockley 2007) is completely disregarded by the DCF approach which assumes that the company makes commitments based on the current status without any room for flexibility to future events.

1.1.1 The advantage of Real Options versus DCF

A solution to the limitations of DCF is offered by other methodologies, namely: Monte Carlo simulations, Decision Trees (DT) and Real Options (RO). The RO approach combines the possibility of dealing with strategic flexibility (as in the DT analysis) with the consideration of the project risk profile (as in the Monte Carlo analysis). In addition to these characteristics the

RO is the only tool that allows considering the change in the project risk profile by changing the discount rate accordingly. The previous chapter described the RO as the most informative and complete method suitable to deal with a complex environment such the pharmaceutical Industry, a business shaped by a high level of market and technical complexity. The paragraph continues by analyzing the main characteristics of RO thus overcoming the limitation of the DCF approach. First of all the RO considers the possibility of a project delivering at the upper extreme, a possibility not accounted for in the DCF. Alongside this, RO combines a more flexible approach that allows managers to avoid the potential of a project delivering at the lower extreme by allowing the possibility of exiting a project. RO thus offers investors the right but not the obligation to execute a business opportunity.

Consequently a key feature of an option is its asymmetrical payoff. This means that additional value is created by including the possibility of achieving a large upside potential coupled with the possibility of limiting the downside by abandoning the investment. Nonlinear payoffs that vary non-proportionally with the underlying, combined with the uncertainty in the future conditions of the underlying, determine the fundamental characteristics of RO.

From a risk management perspective, option pricing provides a direct analysis of the project risk profile. Real option structures quantify risk by assigning a specific probability of outcome distribution.

In practice, RO and NPV approaches are not mutually exclusive but are seen as complementary. The NPV is a special case of RO when there is no flexibility. The DCF analysis therefore captures a base estimate of value while the RO adds on the impact of managing the uncertainties of a given project in a more flexible way.

The DCF valuation, excluding managerial flexibility, leads to valuations that are smaller than the ones based on the RO approach.

The key advantage of the real option valuation is the use of new information about technical performance or market potential so as to strategically respond to change. The real option framework therefore allows for the evolution of investment behavior: from a static process to a dynamic, multi period process.

The interaction between changing conditions in the investment environment and investment/funding decision making is critical. The real option approach is based on the concept that companies define their investment policies, leveraging on uncertainty resolution, thus actively managing their investment strategies.

All these considerations should appease the suspicions of CFO's who liken the RO ap-

proach to a "black box" that tends to overestimate the value of uncertain projects resulting in overinvestment (Van Putten and MacMillan 2004).

Firstly, RO, at its most basic level, is similar in nature to NPV analysis since the value of an option can be seen as benefits less costs while accounting for risk and the probability of occurrence of each variable. Therefore if there is no strategic flexibility, then the real option approach collapses into the NPV value (Mun 2004).

Secondly, in considering RO as an extension of DFC analysis we are able to capture the true value of a project and avoid the trap of underestimation and not investing enough in uncertain but highly profitable opportunities. This in turn would represent the real power of the RO approach (Leslie and Michaels 1997).

If a bad outcome occurs during the development phase of a molecule, the project can be abandoned, thus limiting the development cost. This is formally equivalent to an American put option. A project that can be abandoned (as assumed by the real option approach), is worth more than a project without the possibility of abandonment (as assumed by the the NPV rule).

1.1.2 From DCF to Real Options

The previous section discussed the main characteristics of valuations methodologies DCF (Discounted Cash Flows) and RO (Real Options). The DCF is a static approach that implies that there are no dynamic reactions to changes in the business environment. A decision is taken years in advance without considering the flow of information that will affect the future scenarios. We are considering a "now or never" approach, where either we take the decision now with the information currently available or the possibility expires. Therefore the decision is made based on the current situation without allowing for any reaction to future possible changes.

A step ahead in the direction of a more correct valuation process is made by Decision Tree (DT). This methodology allows including possibility of reaction conditional to the future information flow. Current decisions are taken based on the flow of available information while future decisions will be affected by future information.

The DT maps the series of situations that managers will face and allows taking into consideration the dynamics of decision process. The possibility of actively reacting to new information which is typical of dynamic process allows for flexibility. The tree is developed (from left to right) from the root node to the terminal nodes where the market states are known and

the value of the project can be calculated accordingly. The project value at the root node is estimated working backward the tree (from right to left) using dynamic programming. The value of the project is obtained by discounting the expected values along the tree at the constant risk adjusted discount rate under the assumptions that managers' optimal decisions are maximizing shareholders' value.

The use of a constant risk adjusted discount rate represents a limitation of the DT approach since dynamic decision process alters the risk profile of cash flows. The risk profile is affected by information flow. The risk adjusted discount rate therefore should not be constant since it reflects the impact on the decision process of new available information (Guthrie 2009). This is particularly important in the pharmaceutical business where technical and market information continuously change the risk profile of the project therefore requiring a change in the discount rate.

The final step towards a correct valuation methodology is made by RO. Real Options methods can be applied using various mathematical structures, including closed-form solutions, the most famous being the Black and Scholes (1973), which allows for an exact solution. It is important to notice that the Black and Scholes formula is applicable only to European options, while RO are formally equivalent to American options.[1] This determines the non applicability of the Black and Scholes formula to situations involving the estimate of RO.

Binomial trees have an easy application and focus on the dynamics and consequences of decision processes. The RO discrete construction of a binomial tree is one that is developed under a binomial law with up and down movements that are chosen (by convenience) to recombine. The development of a binomial tree will be explored in more detail later in this chapter.

The RO binomial trees approach uses the same structure of DT: the binomial[2] development of the underlying and backward induction to value the project by identifying the managers' optimal decisions at each node. Nevertheless the RO approach overcomes the limitation of the constant discount rate by applying a methodology that recognizes the altered risk profile of cash flows at each node. By referring to a replicating portfolio mimicking the cash flows of the project implicitly the valuation is determined by the market. The assumption is that

[1] An American option may be exercised at any time before the expiration date and this feature makes it suitable to reflect the Real Option dynamic.

[2] The binomial development is typical of RO, while DT employs branches development not necessarily recombinant.

markets are complete[3] and assets generating the same payoff have the same price otherwise an arbitrage opportunity would exist. Another method for evaluating Real Options, mathematically equivalent to the replicating portfolio approach, is the risk neutral pricing. Under risk neutral pricing the market value is determined as the expected value of the cash flows calculated with risk neutral probabilities (martingale measure probability) and discounted at the risk free rate. The discounting at the risk free rate is possible because the risk adjustment is performed at the numerator by applying risk neutral probabilities. The change in probability measure (from real world to risk neutral probability) does not require investors to be risk neutral, rather it assumes that the asset is traded, and its payoff is replicable thus eliminating the risk.

The replicating assumptions and the risk neutral pricing do not hold in the pharmaceutical industry so therefore a tree is needed where the expected value at each node is calculated with real world probabilities. The expected value is then discounted using a risk adjusted discount rate that is not constant but allows for changes along the tree according to the cash flows' risk profile. In this way we employ the theoretical structure of the RO after verification of the relevant assumptions of a specific business and implement the model accordingly. It is therefore important to verify a model's applicability by ensuring that the assumptions upon which it relies are met within the industry structure, in this case, the pharmaceutical industry.

1.2 Application of Real Options to the pharmaceutical industry: an analysis of the current literature

The RO approach regards investment decisions as a source of opportunity that active management can implement when the appropriate conditions are met. Active management means strategically responding to changes so as to benefit from the evolution of positive scenarios while simultaneously controlling the downside risk. Investment decisions incorporate real options. The term "real options" was first employed by Myers (1977) who identified the possibility of applying option pricing theory to evaluate "real" assets, recognizing the features of call options in some business events as growth opportunities. Myers and Turnbull (1977) extended the concept of real options by identifying a company as consisting of a portfolio of tangible and intangible assets; the latter as real options representing growth opportunities. Mason and Merton (1985) further identify how strategic investment resources, not publicly

[3]Markets are complete when a replicating portfolio can be constructed for any contingent claim.

traded, can be evaluated using real options theory.

McDonald and Siegel's model (1986) incorporates the identification of the optimal time needed to invest in an irreversible project. Important contributions are made by Dixit (1989) and Dixit and Pindyck (1994) who consider the characteristics of investment projects in terms of timing, irreversibility, uncertainty and making analogies with financial options. This theoretical contribution of Dixit and Pindyck (1994) provided the foundations for many advances in RO theory in the 1990's. Progress was made in terms of identifying categories of real options in Trigeorgis (1996) and how these could be applied to other real options models used in a variety of other sectors.

The first applications that used case studies were presented by Brennan and Schwarz's work on natural resources (1985). Oil reserves were first analyzed by Ekern (1985), Paddock et al. (1988) and Cortazar and Schwarz (1997). These applications define the moment where RO started moving from being simply an academic valuation approach to an in-depth methodology with relevance to 'real world' business practice.

In earlier pharmaceutical industry literature, Micalizzi (1999a) presents applications of options to abandon and expand a drug project, with Perlitz, Peske and Schrank (1999) considering applications of sequential compound options on an R&D project. Amram and Kulatilaka (1999) identified learning options in the R&D process. These allow investments to reduce uncertainties surrounding residual development costs. The authors further expand Dixit and Pindyck's theory (1994) by considering the distinction between market price, previously seen as relatively unimportant in the pharmaceutical industry, and private or technical risk.

The importance of the potential practical applications of RO in the pharmaceutical industry is supported by the wide body of literature presented in later years by practitioners. For example, Copeland and Antikarov (2001) explored the impact of uncertainty by modeling a compound real option first with only one source of uncertainty and then with two kinds of uncertainty and two underlyings with the latter offered as an example of a rainbow option[4]. The examples provided are applications of their newly developed theory, the Market Asset Disclaimer or MAD approach, extensively applied among practitioners. Mun's (2004, 2006) exhaustive work on RO together with Copeland and Antikarov's book "Real Options" (2001)" is still today considered a definitive guide for practitioners. Employing the same theoretical framework as Copeland and Antikarov (the Market Asset Disclaimer, or MAD approach which will be later discussed), Mun provides several examples of options to abandon, expand and

[4]Rainbow options or basket options are options with many underlyings

sequential options which have been applied to pharmaceutical businesses. Option parameters, like volatility, are subjectively estimated by considering the project cash flow return volatility, or managements' estimates. These studies have shown that while the approach they all use can differ substantially, in all cases the difficulty starts when the method is implemented because in all cases the real world is more complex and less predictable than the financial one. The difficulty lies in deciding which of those assumptions taken from the financial world hold true in the industrial world, or which of the simplified conditions are acceptable.

Borison (2005) classifies the various RO methods by highlighting their main assumptions, the mechanics of their methods and their applicability. The author identifies five main approaches:

1. **The classical approach.** This is seen as the most direct transposition of the option pricing theory to real assets. Advocates like Amram and Kulatilaka (1999), Brennan and Schwartz (1985), Trigeorgis (1996) and Copeland, Koller and Murrin (2000) considered this approach as the reference for all practitioners' valuations. The classical approach relies on the replicating portfolio, and risk neutral pricing assumptions, and is best described by Copeland, Koller and Murrin (1994):"...a replicating portfolio of priced securities can be found that has the same payout of the option and therefore has the same market value. This is also called a zero arbitrage condition... ". The applications are implemented mainly with the use of the Black-Scholes equation or binomial lattice, relying on the assumption that the underlying is following a Geometric Brownian Motion (GBM).

2. **The Subjective approach.** This approach is often considered to be an extension of the classical approach as it shares its main assumptions in terms of replicable portfolio, no arbitrage condition and the use of standard option pricing tools. What differentiates this approach however is that the inputs for the Black-Scholes formula are subjectively derived from available industry data, or index, instead of coming from market traded assets. The work of Luehrman (1997, 1998) is an example of the subjective approach. Luehrman suggests that the subjective assessment of option parameters can be used as proxy for market values. The author attempts to present an "easy to learn tool...my favorite candidate is the Black Scholes option pricing model, the first and still one of the simplest model" Luehrman (1998). Yet advocating the use of a model based on such a robust theoretical framework, like the Black Scholes, alongside the use of subjective

parameter estimations is likely to generate inconsistent results.

3. **The revised classical approach.** This approach is best represented by the contribution of Dixit and Pindyck (1994). In their work the authors recognize that the assumptions associated with the application of financial options were too stringent and not always replicable in the real world. When such conditions are not met, techniques from the management sciences are best used for project evaluations. In particular, for a project dominated by market risk, the contingent claim analysis can be used. This implies that the assumptions of complete markets are fulfilled.

   For projects where private uncertainty represents the main risk, these are best analyzed by means of decision analysis and dynamic programming. In such cases no complete market assumption is required. Instead private risk is assigned real world probabilities and the discount rate employed in the dynamic optimization is the opportunity cost of capital. With this clear separation between private and market risk, the authors fail to recognize those cases where market risk and private risk are both present and interrelated, such as the pharmaceutical industry. This is done in the Integrated Approach

4. **The Integrated Approach.** The Integrated Approach was first presented by Smith and Nau (1995). It is based on the idea that private risk and market risk are rarely separable, instead they interact. In view of this, an approach is required that analyzes the effects of this interaction. The authors present a methodology that integrates the use of option pricing for risk attributable to the market with decision analysis for the private risk that cannot be hedged. The market risk is evaluated by using a binomial lattice with risk neutral probabilities, while private risk is evaluated using decision trees with real world probabilities.

5. **The Market Asset Disclaimer (MAD) approach.** This is the approach that is the most widely applied by practitioners, including Copeland Antikarov (2001), Mun (2004, 2006) and Shokley (2007). The MAD assumes that the underlying follows a GBM, based on the theory that properly anticipated prices fluctuate randomly (Samuelson 1956). According to the MAD approach the NPV of the project (calculated using a risk adjusted discount rate), without flexibility, is the best unbiased estimator of the market value of a project if it were traded. In this way, the difficulty of finding an asset perfectly correlated is overcome, so practitioners can work under the construct of risk neutral probabilities

while discounting at the risk free rate. The option valuation is based on the binomial approach. A first binomial lattice, representing the evolution of the underlying given by the project NPV, is developed using binomial up and down factors. A second binomial lattice represents the option valuation lattice. While in the first lattice, the lattice evolution of the underlying, the values are obtained in a forward multiplication, in the second lattice, the option valuation lattice, the valuation is performed backwards starting from the end nodes. At the end nodes a value maximization is calculated. For example, in case of an expansion option, this value maximization would be represented by the maximum between expanding less the cost of expansion, versus continuation with the existing business. The value of the existing business is given by the lattice evolution of the underlying. Moving on intermediate nodes, representing different business conditions, the decision between expanding and keeping the option open is made. The value of the option is calculated at each node using risk neutral probabilities and discounting at the risk free rate, back until the starting point. Smith (2005) offered a variation to the MAD approach. His method discounts at the risk free in order to calculate the NPV which is then used as starting node in the binomial lattice.

1.2.1 Specific applications to the pharmaceutical industry

Regarding the specific applications of RO to the pharmaceutical industry, while many authors (both academics and practitioners) have highlighted the option nature of drug development and suggested various applications of RO, the present study will explore the various ways these different methods are implemented. In particular, the present study aims at identifying when the two main frameworks are implemented: either the more financially oriented or the more management science oriented. Here, the first refers to the no arbitrage approach. This approach assumes market completeness; allowing for replicating portfolios, risk neutral probabilities, and risk free discounting. The second method assumes a 'real world probabilities' setting, with a risk adjusted discount rate.

In an early article, Perlitz, Peske and Schrank (1999) used the Geske model (1979) which is an adaptation of the Black- Sholes formula for sequential option valuation. This model was used to evaluate a sequential compound R&D option project in the pharmaceutical industry. Sequential compound options find applications in various industries (i.e. resource extraction, construction, semiconductors, software development) but are particularly relevant in the phar-

maceutical industry. This is because the very nature of the R&D process, where the success in one phase is conditional to the success in the previous one, is more suitably valued as a sequential option. The use of the Geske model implies a risk neutral valuation setting and the use of the risk free rate for discounting.

Micalizzi presents two case studies on Glaxo (Micalizzi 1999a) and Schering Plough (Micalizzi 1999b). In the Schering Plough case the value of an investment opportunity is calculated using a dynamic programming model (Dixit and Pindyck 1994) and a constant risk adjusted discount rate. The Glaxo case refers to the valuation of an abandonment and expansion option within the R&D decision making process. The options' values are estimated with the assumptions that the NPV of the project without flexibility evolves according to a binomial process and the risk neutral setting is applied. Micalizzi's case studies show similarities to the MAD approach where the NPV of the project is considered as best proxy for the project market value if it were traded. The NPV of the project is then modeled as the underlying within a risk neutral valuation framework.

Kellog and Charnes (2000) evaluated the R&D pipeline of a biotech company by first applying a decision tree that was implemented with two different discount rates for development and commercialization cash flows, before applying a binomial tree. The lattice is based on the risk neutral approach of Cox, Ross and Rubinstein (1979) with risk free discounting.

Another project valuation in the pharmaceutical industry was presented by Borissiouk and Peli (2001). Here, the compound option is evaluated using continuum and discrete models, both of which are based on the assumption that markets are complete therefore applying risk neutral pricing. Loch and Bode-Gruel (2001) used decision trees as a means of identifying and evaluating a project growth option that may arise from an R&D program. Like Amram and Kulatilaka (1999), they recognized that R&D pharmaceutical projects are affected mainly by project specific risk for which a replicating portfolio cannot be found. Consequently, the authors propose the use of decision trees to capture risk and flexibility in the pharmaceutical business, where an individual project's payoffs cannot be replicated in financial markets. Triantis and Borison (2001) highlight an example of real option applications to drug development under the risk neutral approach using the biotech company Genentech. Here, the use of risk neutral probabilities to risk adjust the payoffs is advocated for market risk, while subjective probabilities for project specific risk do not need to be risk adjusted because the risk can be diversified away by investors. Rogers, Gupta and Maranas (2002) employed a quadrinomial approach, under the assumption of replicating portfolio and risk neutrality, to evaluate an

R&D project. The reference for the use of a tracking portfolio for a drug is made to (Schwartz and Moon 2000). The same methodology (replicating portfolio and risk neutrality) is proposed in Gupta and Maranas (2004) and in Rogers, Maranas and Ding (2005). The article of Schwarz (2004) presents a model to evaluate a drug R&D project with abandonment option, under the conditions of risk neutrality using Monte Carlo simulations. The paper of Cassimon et al. (2004) presents an R&D valuation for a pharmaceutical company's new drug applications (NDA); a 6 fold compound option obtained as generalization of the Geske's model (1979) is applied under the assumption of risk neutrality. Pennings and Sereno (2010) evaluate an R&D project by modeling the technical uncertainty by means of a Poisson jump and the market uncertainty by a standard diffusion process under risk neutral conditions. Like Copeland and Antikarov (2001) they consider a compound sequential option, but they further implement a model where information arrives continuously and discontinuously over time. This approach thus allows for the possibility of technical failure to occur at any R&D phase. Willigers and Hansen (2008) compare the valuation of R&D projects using 3 different methods: 1) LSM (least squares Monte Carlo) real option valuation based on the methodology proposed by Schwartz (2004) 2) Industry traditional eNPV 3) binomial real option using the MAD methodology of Copeland Antikarov (2000). Approach 1) and 3) share the assumption of risk neutrality.

Authors, mainly working in the area of consultancy, such as Copeland and Antikarov (2001), Mun (2004, 2006), and Kodukula and Papudesku (2006) present various examples and practical applications of the MAD approach in the pharmaceutical business. The MAD approach adopts the same assumptions as the NPV so as to make it an applicable method for real options. This approach surpasses the need to find a replicating portfolio, while still relying on the neutral probabilities setting. This use of risk neutral probabilities, not justified in the pharmaceutical business where projects are not market-traded assets, is employed also by Brach (2003) and Shockley (2007). In their work on RO applications they make the assumption that "a twin security exists in the market that captures exactly the risk and payoffs of the project and allows to construct a risk free hedge" Brach (2003). Shokley (2007) used the replicating portfolio assumption in other case studies within the coal mining industry or the oil industry both of which, unlike the pharmaceutical industry, have market traded prices that make this method viable. In comparison, Villiger and Bogdan (2005) evaluated a pharmaceutical R&D project using, as underlying, the project peak sales. Consistent with the specific business, the authors employ real world probabilities versus risk neutral probabilities, as well as a risk-adjusted discount rate which is kept constant along the tree. Their assumptions is that when dealing with

real business cases, such as the R&D phases of a specific drug under development in the pharmaceutical industry, the replicating portfolio theory cannot be applied since the underlying, the drug under development, is a non-traded asset. This assumption is relevant to the present study which shares the view that "risk neutrality or change of probabilities measures like for financial options lack any justification" Bodgan and Villiger (2007).

The practical applications of RO to the pharmaceutical business show how the different approaches rely mainly on the risk neutral assumption, market completeness and the possibility of finding a replicating portfolio that perfectly mimics the payoff of the underlying project. Here, it is worth noting that to value a RO under risk neutral probabilities is as unrealistic as valuing a hedged business opportunity. Instead, real business conditions must become a part of RO analysis considered as real business opportunities that require a strategic decision approach. Uncertainty characterizes business conditions. When it is resolved through the passage of time, managers can make value creating decisions by choosing the optimal action that maximizes the expected net present value of payoffs (Dixit and Pindyck 2004).

The contribution of the present study is to valuate a compound sequential R&D option, an expansion option and an option to wait by considering how market and technical risk are interrelated. This is the same approach used by Shockley (2007) and Bodgan and Villiger (2007), but unlike Shockley we will not work under risk neutral probability, instead using real world probabilities. Real world probabilities assign to the project a likelihood of commercial evolution and are driven by management experience and marketing research. Risk neutral probabilities based on the assumption that the underlying is a market-traded asset, are an elegant mathematical expedient used to simplify the valuation process, but they fail to represent any business opinion.

Contrary to Bodgan and Villiger (2007), who used real world probabilities and a constant risk adjusted discount rate, the present study will use a discount rate that changes to reflect the different risk profile of each node along a decision tree.

1.3 Real options categorization and their applicability to the pharmaceutical business

The extensive real option categorization provided by Trigeorgis (1996) identifies those RO that are mostly applicable to the pharmaceutical environment. RO are categorized as strategic mod-

els that are applicable to business conditions where uncertainty is a value driver and management has the flexibility to execute strategic options. For example, in the RO model for pharmaceutical R&D phases in drug development, uncertainty is related to the technical clinical trials and market demands, and this creates various kinds of options, which will next be discussed.

Due to the uncertainty of clinical results and market dynamics, a development program can be terminated, thus avoiding incremental cash outflows, this is known as a strategic "*abandonment option*". The option to abandon is particularly valuable for early stage projects that require a significant investment to complete. The value lies in the flexibility of terminating a project that fails to pass an expected threshold.

Sometimes a company can partially recover previous expenses from a project they wish to abandon by means of entering into agreements with biotech or other pharmaceutical partners. This is known as the "*option to abandon for salvage value*" and it involves the potential to exchange contractual ownership agreements of the out-licensing IP (Industrial Patent) rights that are associated with any clinical phase, for salvage value. An abandonment option can be estimated by referring to an American 'put option'. The underlying of the put option is the current eNPV of the project. This is compared with the exercise price represented by the salvage value, that is the eNPV of the deal terms financials. We refer to the eNPV of upfront, milestones and royalties stated in the out-license deal contract.

In practice, the licensor partner will ensure the option to call back the compound (by paying an amount compensating the licensee for the R&D results if specific results are achieved). For example, a company entering an out-license agreement for a compound in phase I can place a "*call back option*" in the contract so that it still benefits if the end of phase II is reached by the licensee. In paying a call back fee, the licensor ensures the possibility of benefiting from the upside (by having the option to finalize the compound and later commercialize it) and limiting the downside (since the licensee takes up the risk of reaching phase II).

If the company decides against an abandonment option, preferring instead to go ahead into the R&D program, the RO framework assumes the characteristics of compound sequential options, or a "*time to build option*". The success of one phase is based on the success of the previous one. The decision to go ahead represents an option on the final option to launch the compound on the market. At each stage, in exercising the option to continue the firm learns more about the technical and market uncertainties as they progressively resolve. After the investment in preliminary R&D, the strategic flexibility to learn and respond evolves from deciding whether or not to develop the compound. The uncertainty and length of drug

development makes this option particularly attractive.

The strategic flexibility of the "*defer the investment*" option is more limited. A firm can create an option to wait and see before making additional investments in the R&D process, thus benefiting only from the resolution of uncertainty. The option to defer can be estimated by referring to an American call option. The decision on when the investment should be made is tackled in the RO approach by relying on the optimal stopping theory applied to American options (Jeanblanc, Yor, Chesney 2009). This theoretical set up allows understanding why the RO approach generally indicates a longer waiting period, in comparison to the NPV rule, when deciding on the optimal investment time.

By assuming a now or never investment, the NPV approach is static. In such context management flexibility and the option of waiting are worthless and no indications are provided on when the investment should be made.

Conversely the RO approach is dynamic and recognizes the strategic value of management flexibility. This implies that the decision to invest is deferred as long as the "time value" of the investing option is positive. The time value represents that part of the option value given by the possibility of future incoming positive news. Under the RO approach therefore, a careful analysis is made before maturity[5], whether the time value is still positive or approaching a zero value. Only in this last case is the option exercise considered optimal and the investment made.

If this is appealing in theory, in practice it is a timely approach and in a competitive industry such as the pharmaceutical business, any time waited is time wasted. Competitive firms working on similar compounds can erode market shares and dramatically reduce the value of a compound, at least in the main indication. In this situation, those depending on an option to defer can miss out on market opportunities while waiting for more favorable conditions[6].

It is common for compounds to presents features that can be used in different indications and in different forms (for example, a drug can be taken either orally or injected). In cases where uncertainty around a drug's development is very high, normally the development of one version (for example the oral version) is developed first, and subsequent investment in another version (the injectable) is postponed, highlighting the potential value of waiting. This

[5]Conversely, under the NPV approach, it is like to exercise an American option as soon as it is in the money, with the consequent sub-optimal exercise.

[6]This aspect will be treated extensively in chapter 2 that highlights how the strategic decision to accelerate projects is paramount.

example is one of the few circumstances in which investment behavior is consistent with the option to defer the investment.

The "*option to expand*" involves the possibility of developing a compound either in a parallel indication or in another form. It can be estimated by considering the analogy of the payoff structure with a call option. The present value (NPV) of the project, including incremental benefits related to expansion, is compared with the investment required to support such expansion. The option to expand has strategic relevance within the pharmaceutical business. In order to explore the potential of future growth, there are R&D programs that are continued despite their negative value (Micalizzi, 1999a). For example the development of an injectable form presents various commercial implications: it opens up hospital channels of distribution, expanding the potential market share and strengthening the brand.

1.4 A discrete-time reduced-form approach: the binomial lattice

In applying the RO (Real Options) approach to real assets, it is important to note that there are some key assumptions which are in common with financial options, such as the parameters structure. This is because the underlying theoretical intuitions behind financial and real options are basically the same. The similarities and differences between financial options and real options, and their applications to the pharmaceutical environment, will next be discussed.

An option is a contract which gives the investors the right, but not the obligation, to acquire or sell underlying assets at a predetermined price. This is true for real options too, where a firm can strategically decide whether or not to exercise a business opportunity. With financial options the underlying is represented by stocks. In comparison, with real options, specifically those in the pharmaceutical business, the underlying is represented by the sales process of a drug, obtained by exercising the option to develop a molecule. A key driver of drug market value is the peak sales, or the maximum amount of sales a drug will generate once launched onto the market. It is important to note that, since we refer to unknown values, peak sales have to be interpreted and understood as "prediction" of peak sales, and as such considered as a random variable.

Managers of life science industry have experience with peak sales predictions and sales curves identified by those peaks. These two concepts form the basis of business practice and will be analyzed in detail by this study. Managers start by estimating peak sales projections and then update those predictions as soon as new data (technical and marketing data) are

available. In practice, during the development phase, scenarios of peak sales evolution are prepared and constantly updated according to the flow of information. During the 6-8 years covering development, many variables come into place making the process underlying the peak sales evolution extremely complex. Factors related to development, such as dose definition, safety, target product profile and to marketing such as pricing, competition, make the valuation estimates an extremely challenging task.

In such complex context, a careful choice of the model to forecast peak sales is required. A reduced form model able to capture the fundamental structure of the problem, that is, the peak sales evolution, is considered the most appropriate approach. Namely, a discrete model such the CRR (Cox-Ross-Rubinstein) model, or binomial model, first developed by Cox, Ross and Rubinstein in 1979, is selected. The choice of the specific binomial model lies in its flexibility to generate scenarios and update prediction of peak sales. The model state variable is represented by the peak sales that develop along the tree generating various possible scenarios. In this way, at the end of the R&D process the value of peak sales that can be met under various path realizations are available. The next step refers to the forecast of the entire sales curve. Each peak sales identifies a sales curve whose dynamic can be represented by a Geometric Brownian motion process (GBM). The following sections illustrate how peak sales scenarios are modeled and from there how the entire sales curves are calculated.

1.4.1 The binomial model to generate scenarios about future peak sales

The model is discrete as it has a finite number of time intervals, each of the same length. It is referred to as ”binomial” because each node of the decision tree represents the same structure; with either an ”up” or a ”down” movement of the underlying which is determined by the volatility parameter. The nodes are such that each state of the economy can move in one of two directions: either moving to an up state or a down state (Roman, 2004). The movements at each node are independent from the previous ones. The model has been selected to generate scenarios about future peak sales, whose prediction is indeed a challenging task.

Originally developed for financial stock returns, the structure can be easily adapted to simulate scenarios describing the changes in future peak sales. The uncertainty associated with the peak sales dynamic is characterized by using probability theory and is expressed by a random variable (Baz and Chacko, 2004).

The model implies that the random variable X (representing peak sales) can move up

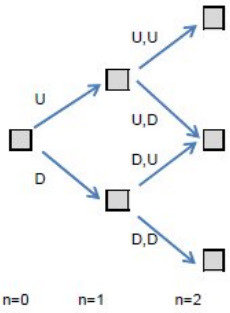


Figure 1.1: Binomial tree

with probability p or down with probability $1-p$, in accordance with a Bernoulli scheme:

$$X = \begin{cases} U & \text{with probability } p \\ D & \text{with probability } (1-p) \end{cases}$$

where $D = 1/U$ to ensure that the tree is recombinant.

If we consider a two time steps, $n = 2$ as in figure 1.1 the final economic conditions can be achieved through various routes; either an up state followed by another up (U,U) or an up state followed by a down state (U,D). Alternatively it can take the other direction, for example a down state followed by another down (D,D) or a down state followed by an upstate (D,U).

The final states can be represented by the probability space $\Omega = \{U, D\}^2 = 4$ states. We make the assumption that the tree is recombinant, that is the nodes U,D and D,U both identify the same state of nature. The final states therefore reduce themselves to the value of three, as in figure 1.1. The structure can be replicated for an "n" number of steps leading to a cone of uncertainty[7] that tracks, at each node, the various states an underlying can assume.

After having defined the procedures on how to generate peak sales scenarios, the next step is to define the real world (or objective) probabilities "p" that peak sales will assume an 'up' movement.

As previously discussed, the framework underlying financial options cannot entirely be applied to real options in the pharmaceutical business because the assumptions underlying financial options, such as the replicating portfolio assumption, do not hold for the pharmaceutical industry. For real options, the main assumption behind the construction of a risk free portfolio would be that the underlying (the drug) is traded, or other assets are accumulated

[7]The cone of uncertainty is explained through the idea of uncertainty increasing over time (Mun 2006).

that perfectly correlate with the drug so as to exactly "span" the drug asset value (Dixit and Pindyck, 1999). Neither of these conditions can be met in the pharmaceutical business. As a consequence, the risk neutrality change of probability measure and the use of risk free as discount rate do not hold. Instead, real world probabilities must be utilized as well as a risk adjusted discount rate.

In the pharmaceutical business, risk neutral probabilities (q), used to construct a risk free portfolio in the financial options setting, need to be replaced by real world probabilities (p) using real option analysis. This significantly differs from other businesses where the underlying (price of oil, commodities, gold) is traded therefore permitting the use of risk neutral probabilities (q).

In the context of the pharmaceutical industry, real world probabilities "p" describe how predictions of peak sales are updated over time. Fluctuation in the update of the peak sales dynamic of a drug generates risk for the option holders that need to be rewarded at a risk adjusted rate (r_a) which bears a premium for non-diversifiable risk. Non-diversifiable risk contains a market component that cannot be diversified away by investors' decisions. Diversification is important for the investor who should aim at owning a well diversified portfolio. At a firm level a lack of diversification exposes the company to business risk related to possible failure of molecules in the pipeline. In this context, a company working on respiratory drug inhalation devices for asthma could reduce risk by investing resources in other drug delivery devices for the same condition (asthma). A characteristic of the pharmaceutical business is that non-diversifiable market risk is not easily separated from technical diversifiable risk during all the phases of the R&D process. Calculating the risk adjusted rate to discount a project's cash flows and obtain a real option value at each stage of the R&D process will be later discussed.

In financial options, the strike price represents the fixed price at which the investor can exercise the option and buy (in the case of a call option) or sell (in the case of a put option) the underlying. In comparison, pharmaceutical options use the expected development costs that a company needs to sustain in order to bring a molecule from R&D to market launch. These costs present a low level of uncertainty and assume a deterministic path which runs symbiotically with the conditions experienced at each phase of development of a product within the pharmaceutical industry. For example the experience gained in technical operations, empowers an adequate level of estimation on the costs of goods sold. Similarly, knowledge gained through clinical studies offers further information on how to plan for future development costs.

As in the case of financial options, with real options there is a time of expiration that is a

point in time at which the option is no longer valid. For real options, this time coincides with the life span of the project, which in the pharmaceutical industry averages about 6-8 years and corresponds to the maturity of the option to invest. Contrary to financial options, increasing the time to expiration does not increase the value of the real option. The longer it takes to launch the higher the amount of loss experienced from late market entry, patent expiration and the impact of competition (Brach, 2003).

A closer look at the cone of uncertainty shows that the higher the value σ, the wider the spread at the extreme end of the binomial lattice. If the value σ is very small then the lattice tends to approximate a straight line. The parameter σ represents the volatility of update of peak sales scenarios identified by the pharmaceutical managers depending on market and technical uncertainty. The absence of uncertainty implies that optionality has no value, then the business case would be better analyzed via a DCF (Discounted Cash Flow) application (Mun, 2004). Volatility is another parameter that does not share the same impact as it does in financial options, where an increase in volatility increases the value of the option. Volatile market conditions may increase the value of the real option by increasing the upside potential of the drug on the market, but technical uncertainty tends to reduce the value of the project by increasing the time to launch resulting in a lost competitive market advantage. Current existing models do not consider the existence of such volatility determined by technical uncertainty. A numerical example presented in this study covers both kind of uncertainty.

After introducing the theoretical framework underlying the model, it is next possible to specify the parameters the model requires to finalize lattice development:

The up and down steps are defined by:

$u = e^{\sigma\sqrt{\Delta t}}$

$d = 1/u$

That the d (down) factor is the reciprocal of the u (up) factor ensures the recombinant property of the tree. The value of Δt represents the discrete time interval. The parameter σ appearing in the formula, represents the standard deviation, or uncertainty on peak sales prediction. Given the complexity of the forecasting process taking place during the development of a drug that will not be launched for another 6-8 years, the value of σ is kept constant along the tree. An estimation of σ based on actual forecasting data will be later presented.

The real world probabilities "p" in discrete settings is defined by Bodgan and Villiger (2007):

$P(Pk_{t+\Delta t} = u \cdot Pk_t) = \frac{(1+\mu)^{\Delta t} - d}{u - d} = p$

$P(Pk_{t+\Delta t} = d \cdot Pk_t) = 1 - p$

where u and d represent the up and down factors respectively and Pk is the expected value of peak sales.

The parameter μ used in the calculation of real world probability represents the drift of the peak sales forecast. Due to the complex and uncertain forecasting process, a simplified approach is applied in modeling the drift. In this case the assumption is that the drift of the market, defined by marketing analysts as the market "regimen growth rate", is the best proxy for the drift of the peak sales forecast.

1.4.2 Sales curves identified by the peak sales

The previous section analyzed how peak sales scenarios are modeled. At the end of the R&D process the values of peak sales that can be met under various path realizations are obtainable. Once peak sales are available, the sales curve is calculated following a percentage structure based on empirical data. In this way each peak sales identify an entire sales curve.

A further assumption is that the sales curve dynamic follow a Geometric Brownian Motion process (GBM) with constant volatility. The change in the sales process (V_t) following a GBM can be expressed by:

$$dV_t/V_t = \mu_t^V dt + \sigma^V dz_t$$

where μ_t^V represents the positive drift of the sales process assumed to be piece wise constant, and σ^V its volatility assumed to be constant.

The equation is made up of a deterministic element, $\mu_t^V dt$ expressing the change over time in a deterministic way and a stochastic element $\sigma^V dz_t$. The value dV_t represents the change in the sales process value V_t in a small interval dt and dz_t represents an increment of a brownian motion, known as a Wiener process and it is a normally distributed random variable such that $dz \sim N(0, dt)$.

Standard practice assumes that the sales curve of a commercial product is structured in such a way as to represent percentages of Pk (the peak sales), where the peak sales Pk is defined as $E_0^P[\sup_{[0,T]} V_t]$, that is expected value of peak sales.

This is equivalent to say that expected sales in year T, as seen from time 0 are expressed as:

$$E_0^P[V_T] = V_0 e^{\int_0^T \mu_s^V ds}$$

The expectation is calculated over historical probability P, since we are working with a P brownian motion. The assumption is that μ_s^V is determistic and piecewise constant changing every year to reflect marketing predictions. The choice of a positive drift implies that sales are expected to grow in the long run. In reality sales are growing only up to patent expiration, after expiration of the compound's patent, the sales dynamic is generally showing a clear decrease. This case is best represented by a positive drift followed by a negative drift[8]. The model presented in this chapter is based on the simplifying assumption of business practice that sales drop to zero after five years of patent expiration.

1.5 The volatility parameter

So far two kind of volatility parameters have been introduced: the volatility of peak sales predictions σ and the volatility of the entire sales curve σ^V. A discussion of both parameters is presented in the current and following section.

We have seen how the volatility parameter σ affects the amplitude of the cone of uncertainty as well as determining the range of values the peak sales can assume.

To understand the specific characteristics of σ as volatility of peak sales predictions, it is important to first consider the specific forms of risk that are exclusive to the pharmaceutical industry.

In the pharmaceutical industry risk stems from internal and external forces. Internally there is technical risk related to the R&D phases, production risk and the risk associated with the passing or failing of clinical trials. Externally, risk is associated with market uncertainty which relates to the commercial potential of the drug once launched on the market. This in turn is affected by the competitive situation, regulatory risk and the risk associated with drug reimbursement.

Practitioners such as Kodukula and Papudesku (2006) consider these two kinds of risk separately by first calculating the option value (external) and then applying the technical probabilities of success (internal). Other authors, (Berk et al. 2004, Shokley 2004, Bodgan and Villiger 2007) argue that it is better to consider them jointly, because while the two kinds of uncertainties could seem unrelated, (market risk only enters the equation once a product receives the FDA approval and is ready to be launched), in reality they strongly interact during all development processes. The profitability and market value of the project are constantly

[8]This scenario is analyzed in detail in Chapter 2.

monitored during the development phases to take into consideration competition and market dynamics. In this way only those projects showing technical success and an adequate market potential are developed. This implies that the option value has to be calculated by integrating the option solution lattice with the technical probabilities of success.

Most authors argue that this latter, more integrated, approach is superior. During the R&D process there is a continuous stream of information becoming available, not only about the likelihood of successful completion, but also in term of a target drug's definition or target product profile (TPP). New details on the target drug may lead to modifications in the R&D program, in technical uncertainties and ultimately in market uncertainties as a new customer target may need to be identified. This in turn will lead to a revision of the technical PoS (probability of successfully moving to the next phase), and the future expected value stream of a drug's market potential.

The parameter σ reflects both sources of volatility where market risk interacting with technical risk is captured through the binomial tree of the underlying peak sales. The resolution of technical risk is captured as exogenous shock at the end of each phase according to the following expression:

$$PoS \cdot \max[Underlying – K, 0] \tag{1.1}$$

The above expression takes into account the probability of successfully moving to the next phase (PoS). This is multiplied by the payoff of a continuation option if there was no technical risk $\max[Underlying – K, 0]$.[9] The option solution lattice is thus integrated with the technical probabilities of success.

It is important to emphasize that technical uncertainty is progressively reduced during the development phase. The decisions at each phase depend upon the resolution of both risks (technical and market). For example, there may be situations in which the product passes the clinical trials but the company may still decide to cease development because the market potential is not adequate (Shokley, 2004).

[9]The decision whether to continue or abandon the project can be taken only at the beginning of a development phase

1.5.1 Estimation of volatility peak sales σ, based on actual values

Volatility estimation is a very challenging task. Analysis of the current literature presented by practitioners provides estimations of sales process volatility. As an example Bodgan and Villiger (2007), suggest using a percentage moving in a range from 20% to 50% as volatility of the peak sales. In comparison, authors such as Borissiouk and Peli (2001) consider the volatility used to compute the option value of a molecule as the volatility of the project returns. The authors simulate the distribution of returns assuming price and market share as the main drivers of project uncertainty. The simulation shows a volatility of the specific project returns of about 49%. Pennings and Sereno (2010) recognize the difficulty in estimating the volatility due to the non-traded nature of the underlying. They suggest using, as a proxy, the stock price volatility of a listed biotech company producing similar products. Based on these historical stock prices, the volatility of the project value proposed is in the range of 23%-57%.

Given the impact of the σ parameter on the analysis, the choice of a volatility parameter needs to be extremely accurate. As previously shown, volatility expresses not only the uncertainty around the peak sales estimate and general market uncertainty, but also the technical uncertainty surrounding completion of clinical trials. This makes the analogy with financial options less than ideal, but it responds to the business dynamic that makes necessary periodic revisions of sales forecasts by the management team. About three to four times a year (when clinical results becomes available) peak sales estimates are adjusted to reflect market potential, competitors' information and clinical trial results. This leads to a continuous revision of the potential commercial value of the drug.

To estimate the volatility of the peak sales we focused on the Therapeutic Area (TA) of interest, taking into consideration all other projects in the portfolio pipeline for the specific TA. The idea is that there is an underlying sales structure common to all compounds in the specific therapeutic area and each determined by the specific marketing assumptions underlying the sales forecasts of that market.

The present study aims at calculating the volatility estimate for the TA of Infectious Disease (ID). The available data consists of 14 sets of update of forecasts for molecules currently in the ID portfolio (see Appendix 1). It is important to note that peak sales updates represent different trajectories on the tree. Changes in the updates are calculated and their standard deviation represents the volatility of update of the peak sales scenarios.

Peak sales of each curve are identified and then standardized over the mean curve to

ensure the comparability of forecasts for the different molecules: $Z = Pk/Mean\ curve$.

The volatility is calculated based on the relative changes of Z adjusted by the squared root of n, where $n = 3.5$ and reflects the average periodicity (3-4 times a year) within which the forecasts are revised to reflect clinical results, interim analysis results or market information. Interim analysis is part of clinical study design and is performed based on data that is deemed sufficient to draw preliminary, but not necessarily complete conclusions. In this way management is able to decide beforehand whether to continue or not the clinical trial.

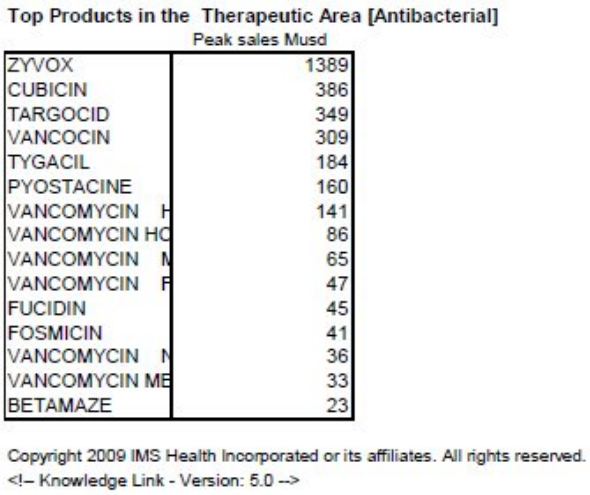
The assumptions are that the quarterly updates of standardized peak sales are independent, identically distributed random variables (Benninga, 2008), therefore $Var(r) = 3.5\sigma^2$, while the standard deviation of the annual rate becomes $\sqrt{3.5}\sigma$ period.

Final calculations lead to a value of volatility of about 29% (see Appendix 1).

This creates a mean line formed from the increments of the peak sales curves which is used as starting node of the binomial expansion. In this way, all data points of the curve (not only the peak) are taken into consideration and changes or increments with regards to the average line are assumed to be IID distributed. After all scenarios are predictions of future peak sales. Predictable component of scenarios is already embedded in the drift, what is left is the unpredictable component of the update of peak sales.

Based on management estimates, a decision is made to maintain the values of volatility (29%) obtained from the data of all molecules currently in the portfolio. The high volatility estimate reflects the fact that single projects carry a big uncertainty. This uncertainty refers to two factors. The first is the market uncertainty reflecting the competitive landscape, and the drug's position in the market and subsequent profitability. The second factor is the technical uncertainty that refers to production risk and the likelihood of successfully moving to the next stage of development.

This latter occurrence is modeled as a 'sudden event' due the nature of information flow. Information does not arrive in a smooth fashion, but rather in a sudden form when clinical data becomes available. This happens at the end of each development phase or when Interim Analysis results are available and the flexibility of the tree accommodates for the new information and unpredictable events.



Top Products in the Therapeutic Area [Antibacterial]

	Peak sales Musd
ZYVOX	1389
CUBICIN	386
TARGOCID	349
VANCOCIN	309
TYGACIL	184
PYOSTACINE	160
VANCOMYCIN H	141
VANCOMYCIN HC	86
VANCOMYCIN M	65
VANCOMYCIN F	47
FUCIDIN	45
FOSMICIN	41
VANCOMYCIN N	36
VANCOMYCIN ME	33
BETAMAZE	23

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Figure 1.2: IMS - Top Products in Antibacterial

1.5.2 Estimation of volatility of the entire sales curve σ^V, based on management's estimates

Once the prediction of peak sales have been developed, predicted sales curve identified by a given peak are considered.

The volatility of predicted sales σ^V can be derived from managers experience. Obviously managers cannot provide precise estimates on the volatility of the sales curve but instead use "experienced intuitions" about the likelihood of reaching certain level of sales. This approach, which is subject to some limitations, still can lead to a range of estimations that can be used to provide the basis for more accurate calculations.

The main limitation is that such estimates are based on subjective interpretations of market analysis and available information from existing databases like the IMS Health, a leader in market research for the pharmaceutical industry (fig 1.2). The assumption behind management estimations is that sales follow a lognormal distribution, which might not hold in practice.

Shockley (2007) argues that such an approach is oversimplified and allows only vague volatility estimates. Various scenarios, in terms of sales realization, are considered and management is required to attribute probabilities of reaching that specific level of sales based on subjective knowledge. For example, a management team may be asked to calculate the probability of reaching a value Z of sales. Based on experience and some specific market data they will assess the likelihood of different scenarios occurring, thus implying various levels of sales.

Assuming therefore that, according to management estimates, sales follow a lognormal

distribution, it is possible to quantify the probability of having future sales (V_T) worth at least a value Z based on the following:

$$Pr(V_T > Z) = Pr(\ln V_T > \ln Z) =$$

$$Pr\left(\frac{\ln V_T - \ln V_0 - (\mu^V - (\sigma^V)^2/2)T}{\sqrt{(\sigma^V)^2 T}} > \frac{\ln Z - \ln V_0 - (\mu^V - (\sigma^V)^2/2)T}{\sqrt{(\sigma^V)^2 T}}\right) =$$

$$1 - \Phi\left(\frac{\ln Z - \ln V_0 - (\mu^V - (\sigma^V)^2/2)T}{\sqrt{(\sigma^V)^2 T}}\right) = \Phi\left(\frac{-\ln(Z/V_0) + (\mu^V - (\sigma^V)^2/2)T}{\sigma^V\sqrt{T}}\right) =$$

$$\Phi\left(\frac{\ln(V_0/Z) + (\mu^V - (\sigma^V)^2/2)T}{\sigma^V\sqrt{T}}\right).$$

This follows from $1 - \Phi(x) = \Phi(-x)$ where Φ is a Gaussian cumulative distribution function. Here Z represents a specific sale value, V_0 is the initial level of sale when the product is launched, μ^V is the drift of sales before patent expiration and T is the time of patent expiration.

Conversely the probability of having a sale value smaller than a value Z is given by:

$$\Phi\left(\frac{\ln(Z/V_0) - (\mu^V - (\sigma^V)^2/2)T}{\sigma^V\sqrt{T}}\right)$$

Scenarios are considered in term of best, upside, base and downside realizations. The parameter σ^V is varied until the probability of getting closer to management estimates is achieved.

Figure 1.3 shows the results of the simulations. For example managers' estimate of an upside case scenario is about 5%. This estimate does not match exactly the lognormal distribution, but it is best approximated by a probability of about 14% corresponding to a volatility of 25%. In general management estimates are matched by a volatility in the range of 25-35% with evidence of a value closer to the lower end of the range. The example suggests that in the specific case managers' expectations when developing predictions of peak sales, as calculated in section 1.5.1, are close to the volatility expected in the sales curve dynamic.

Once the volatility of predicted sales σ^V and the drift μ^V are available, sales curves trajectories could be simulated using Monte Carlo simulation obtaining different scenarios of sales curves, which in turn may be used to assess risks associated to poor sales trajectories[10]. Furthermore confidence interval could be constructed around the sales curve, informing about the range of values we expect to find the realized curve with a certain confidence level.

[10]The output of a Monte Carlo simulation is a frequency distribution chart showing the probability of occurrence of the sales variable. In this context a worst case scenario indicates for example that a certain level of sales is

Scenario	Sales level	Management estimates *	Probability implied by volatility			
			25%	35%	60%	70%
best case	>1500	1%	1.0%	3.0%	5.7%	5.7%
upside case	>700	5%	13.7%	16.1%	14.4%	15.3%
base case	>250	50%	72.1%	58.3%	35.8%	29.5%
downside case	<230	30%	30.4%	40.1%	57.9%	63.8%

* Management estimates refers to scenarios not covering the entire probability space

Figure 1.3: Management estimates of volatilities

1.6 An R&D project – Introduction

The decisional processes in the R&D department have the responsibility, together with the business division, to identify and then develop the right molecules. It is worth summarizing the stylized facts and characteristics of the pharmaceutical R&D in order to show how investment decisions have commonality with decisions to exercise an option:

1. Uncertainty exists with respect to the length in time of the R&D process which is unknown initially but on average takes around 6-8 years depending on the specific compound.

2. R&D investments costs are irreversible; they cannot be recovered or undone if conditions change.

3. The development process is split into multiple phases. At each phase, based on the information available, management can choose whether to continue development or not. In this strategic decision-making process, the main challenges refer to the uncertainty surrounding the technical capabilities of developing the drug, the drug market potential and financial feasibility. Such uncertainties resolve over time as the investment is sequentially completed.

Drugs in R&D phases go through a sequential structure compound option that is evaluated using a real option model. Various authors (Dixit and Pindyck 1994, Shockley 2007, Copeland and Antikarov 2001, and Brach 2003) identify the sequential nature of the R&D decisional process in the pharmaceutical business. The key factor in these options is the possibility

achieved with a certain likelihood.

of ceasing investment if the value of the drug is not viable. In this way the completion of one phase, gives the option to complete the next phase, and so forth.

The implementation of the model is done by applying the binomial tree technique due to its advantageous characteristics. The binomial model is flexible and permits analysis of complex situations (e.g. staged investments). It also offers a multi-period view which enables visualization of the changes in the underlying, so that subsequent decisions about options exercise at different points in time are more readily available.

The use of binomial lattices (or trees) follows specific steps of analysis. Firstly, after the calculation of the relevant parameters, the tree is developed to reflect the cone of uncertainty. Here, the values that the peak sales estimates assume over the time period span from the beginning of the R&D process (the route node) to the Registration date (the terminal nodes). Assuming a time step (Δt) of 1 year, the algorithms used to simulate the up (u) and down (d) movements defining the cone of uncertainty (Hull, 2003) are:

$$u = e^{\sigma\sqrt{\Delta t}} \quad d = e^{-\sigma\sqrt{\Delta t}}$$

where σ is the volatility of peak sales update.

1.6.1 An R&D project: the valuation process

Considering a discrete case, the peak sales Pk will grow on average as $Pk(1+\mu)^{\Delta t}$. Although the rate at each peak sales predictions are updated could be time-varying, it appears a challenging task to determine a suitable dynamic of such a parameter μ. Therefore, the parameter μ is kept constant throughout the binomial tree. The volatility parameter σ determines the amplitude of the up and down movements. The higher the uncertainty expressed by σ, the wider will the cone of uncertainty be realized within the tree's development.

The probability "p" is the real world probability that determine the occurrence of an up movement and (1-p) of a down movement (Neftci 2000). The discrete formulae introduced in section 1.4.1 are according to Bodgan and Villiger (2007):

$P(Pk_{t+\Delta t} = u \cdot Pk_t) = \frac{(1+\mu)^{\Delta t} - d}{u-d} = p$

$P(Pk_{t+\Delta t} = d \cdot Pk_t) = 1 - p$

If we assume to develop the lattice in a multiplicative way, during a time step Δt peak sales Pk can only move up by the U factor or down by the D factor:

$$Pk_{t+\Delta t} = \begin{cases} u \cdot Pk_t \text{ with probability } p \\ d \cdot Pk_t \text{ with probability } 1-p \end{cases}$$

The development of the tree provides knowledge associated with the values assumed by peak sales at the end nodes. These correspond to the end of development, when the drug is approved by a health authority and is ready to launch on the market. The binomial tree development allows simulating scenarios on peak sales values expected at the end of the R&D process. Each peak sale value identifies a sale curve described by a GBM. The NPV value of the project is then estimated as if no technical uncertainty exists, and the compound has already been launched on the market. The NPV of the project is calculated using a constant risk adjusted discount rate which compensates investors for systematic market risk.

The value of the project with the option is calculated at each time step by applying backward induction. Rollback or backward induction is a process used within dynamic programming; a technique used to solve real options problems when a replicating portfolio cannot be found. The contingent claim method involves the definition of a replicating portfolio. This method's assumptions such as complete financial markets, portfolio replicability and risk neutral probabilities, do not however hold true in the pharmaceutical business.

Dynamic programming allows companies to optimize their investment decisions during times of uncertainty. At the final node of the tree, the NPVs of a project correspond to the different peak sales realizations, or paths, along the tree. Working backwards through the tree, integrating the NPVs of the project within the different development phases, all possible investment opportunities together with their corresponding payoffs are calculable. Since the various NPV scenarios at the terminal node are known with certainty, it is necessary to go back through the tree to the initial node and recursively consider, at each node, the optimal alternatives. This is, in essence, the dynamic programming methodology. It works by assuming that all past information is captured in current market values at time t. Simultaneously, all future decisions are optimized on the basis that a project's market value reflects both upside and downside movements at time t+1 (Guthrie, 2009).

To reflect the specific decision processes at each R&D phase, two states encountered along the tree must be considered; the end of each development phase and the beginning of each development phase.[11]

At the end of each development phase, the PoS (Probability of successfully moving to the

[11]The R&D decision can be made between the two points in time.

next Phase) is applied. For example, the potential market value of a drug "V_{T_E}" at the end of each development phase [12] is defined based on the following formula (Villiger and Bodgan 2005)[13]:

$$V_{T_E} = PoS \cdot (pV^{up}_{T+\Delta t} + (1-p)V^{down}_{T+\Delta t}) \cdot 1/(1+r_a)^{\Delta t} - I \cdot (1-t_c) \tag{1.2}$$

where:

PoS = (probability of successfully moving to the next phase)

p= real world probability of moving upward

$(1-p)$ = real world probability of moving downward

r_a = project risk adjusted discount rate; this is not a constant value but one that changes along the development cone of uncertainty

$I \cdot (1-t_c)$ = ongoing development expenses, net of tax (t_c)

Formula (1.2) represents an expected value that is available only if the phase is successfully completed: this happens with a likelihood expressed by the PoS.

The beginning of each development phase, or when Interim Analysis results are available, reflects a decision point. The decision over whether to continue or not is determined by comparing the beginning phases' development costs "I" net of tax (t_c), with the potential market value of the drug "V_T", realizing a net value ("Net V_T") which is given by:

$Net\ V_T = \max\{V_T - I, 0\}$

where the Net Value is calculated at time T according to formula (1.3) and t_c is the company marginal tax rate.

$$Net\ V_T = \max\{[(pV^{up}_{T+\Delta t} + (1-p)V^{down}_{T+\Delta t}) \cdot 1/(1+r_a)^{\Delta t}] - I \cdot (1-t_c), 0\}. \tag{1.3}$$

1.7 An example of a compound option: Infectious Diseases Therapeutic Area in R&D

The remainder of this chapter will expand on the previously mentioned example of the infectious diseases (ID) therapeutic area (TA) subjected to the R&D phase as point of reference. This example is relevant to the present study as it represent the valuation of an R&D project using a sequential compound option structure. More specifically, this chapter will focus on a

[12] The probability of successfully moving (or failing) is accounted for only at the end of the phase when the completion of the development phase becomes effective.

[13] The formula has been modified to consider the tax impact on investment costs.

	Time (years)	Costs ($Mio)	PoS
Phase 1	1	12	66%
Phase 2	2	56	64%
Phase 3	3	117	58%
NDA filing	1	5	95%
Launch	1	40	100%
PoS cumulative			23%

Figure 1.4: Development Costs and PoS

compound in the TA ID, which exists within the antibacterial segment. The example is a topical antibacterial cream intended for use as a treatment for post-injury skin infections the data from which is based on peak sales figures drawn from existing companies operating within this area. The figures are used purely illustratively for the purposes of fulfilling the aims of the present study. The antibacterial segment is made up of drugs that target bacteria to either destroy or inhibit their growth. If the compound is at the beginning of phase 1, to successfully complete the R&D process the firm must complete four discrete phases; from completion of phase 1 to NDA filing. Each phase has a specific duration, probabilities of successfully moving to the next phase (PoS) and cost associated with it, as shown in figure 1.4.

In this example, further relevant information for business case development is as follows:

- the pre tax operating profit = 49%
- the company marginal tax rate=10%
- marketing expenses = 15%
- the risk adjusted discount rate r_a or WACC =8%.

It is assumed that the project risk is equivalent to the company risk once the drug is launched onto the market. It is accounted for by a constant risk adjusted discount rate of 8%. In contrast, alongside the development cone of uncertainty the risk adjusted discount rate changes to reflect the levels of risk associated with the various conditions at each position on the binomial tree.

1.7.1 The calculation of the risk adjusted discount rate during the development phase

Moving along the development's cone of uncertainty, the risk adjusted discount rate changes to reflect the riskiness of the project in terms of cash flows. The discount rate assumes different values at different positions along the tree. The cost of capital is therefore not constant as noted by various authors such as (Koller, Goedhart and Wessels 2005, Shokley 2007, Copeland and Antikarov 2001) but changes according to the evolution of the option risk profile along the cone of uncertainty.

In choosing an appropriate discount rate, Dixit and Pindyck (1994) discuss a discount rate that compensates the holders for (non-diversifiable) risk. In the present example, the optimization process, implemented by dynamic programming at each node of the tree, alters the risk profile of cash flows requiring the discount rate to change. The discount rate used for projects without flexibility is therefore not appropriate for analyzing a project that includes flexibility (Brandao, Dyer and Hahn 2005, and Shockley 2007), such as the present example in the pharmaceutical R&D stage. According to Trigeorgis (2001) "the fundamental problem lies in the valuation of investment opportunities whose claims are not symmetric or proportional and whose discount rates vary in a complex way over time ..."

As described by Reyck, Degraeve and Vandenborre (2006) having the flexibility to stop the project and exercise an abandonment option changes the project cash flows and risk profile to $CF_f = \max(CF_{wf} – I, 0)$, where:

CF_f = cash flow of the project with flexibility

CF_{wf} = cash flow of the project without flexibility

I = required investment

In incorporating the ability to react to new information, managers can take actions that benefit from 'good news' while mitigating the impact of 'bad news' . In this way an asymmetric payoff is determined since the upside and downside scenarios can trigger a different decision, for example choosing to either continue or abandon the project (Guthrie 2009).

This explains why the present value of the option cash flows, or project with flexibility, cannot be calculated using a constant risk adjusted discount rate. Instead, a discount rate that mirrors the underlying uncertainty and the managerial flexibility to respond is needed[14].

[14]The project risk profile changes as technical and market risks change, requiring appropriate future business decisions. Technical and market risks are highly interrelated and consider the change in state of competition when time elapses.

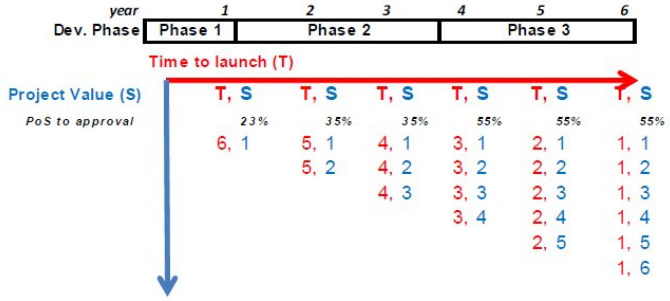

Figure 1.5: Technical risk and market risk for each state of nature

In the case of figure 1.5, during the development phase (year 1 to 7)[15] technical risk is inseparable from market risk, since both forms of risk are interrelated. After launch (year 8 onwards) technical risk is resolved and only market risk remains.

It is assumed that the appropriate risk adjusted discount rate used by a company for a project without flexibility is Weighted Average Cost of Capital (WACC) of 8% and that the project correlates with the company's cost of capital (Alleman 2002). The WACC of 8% is obtained by applying CAPM (Sharpe, 1965) to estimate the cost of equity assuming the following factors:

r_f (risk free)= 3.8% representing a 20 year zero coupon bond matching the project duration and cash flows currency.

Beta[16] (Industry Beta)= 0.9 and MRP (Market Risk Premium) = 5%[17]. The Industry Beta is unlevered and relevered to the company's target capital structure $\frac{D}{D+E}$. The cost of debt is estimated based on the company's credit rating.

During development (from Phase 2 to Phase 3) , the discount rate changes to include a premium for the riskiness at each uncertain state of nature (figure 1.5) where levels of technical and market risk are interrelated and ranked according to a scale of values from 1 to 6 . We assume a time and a state varying discount rate, where each state is identified by a triplet T, P, S. These variables T, P, S identify the factors that affect the cash flows risk profile. Thus the discount rate function $W = f(T, P, S)$ is defined as an equation in three variables:

$$W = aT + b(1/P) + cS + K \tag{1.4}$$

[15] In the specific example year 7 represents the year of the drug Registration.

[16] Source: Bloomberg. The industry beta is preferred to avoid potentially large estimate errors when estimating betas of individual stocks. This concept is treated extensively in R.A. Brealey and S. Myers 1996.

[17] Source: Koller, Goedhart, Wessels (2005)

year	1	2	3	4	5	6
discount rate	23.1%	19.2%	16.7%	13.1%	10.6%	8.1%
		21.0%	18.5%	14.9%	12.4%	9.9%
			20.3%	16.7%	14.2%	11.7%
				18.5%	16.0%	13.5%
					17.8%	15.3%
						17.1%

Figure 1.6: The discount rate structure along the tree

with domain defined by the set of triples (T, P, S) of the T, P, S space that satisfies equation (1.4). Only triplets (T, P, S) that satisfy equation (1.4) are possible, given a certain level of discount rate W.

We define T=time to launch (in years), P= Probability of Approval, S=Project value as determined by the Target Product Profile (TPP), K = constant covering additional macroeconomic factors (like risk-free rates, exchange rates or political risk) that might affect the discount rate, as well the identified factors. The intuition suggests that the impact of time expressed by parameter a is the most important. Long time to launch means higher technical and market risks. Project value, indicated by parameter c, reflects market risk and competitors dynamic. Also, the ratio $1/P$ suggests that higher probabilities of technical success lead to a smaller discount rate W.

Input quantities are assumed to be non-negatives, $T \geq 0, P > 0, S \geq 0, K \geq 0$.

Given the boundary conditions :

1) $W \geq$ risk free rate 2) $T \geq 0$, $S \geq 0$, 3) $0 < P \leq 1$

parameters are calibrated to obtain discount rates values consistent with market practice and the function for the specific project becomes: $W = 2.5T + 1/P + 1.8S + K$, with $K = 2$.

Based on the values of T, S as ranked in figure 1.5, the PoS values stated in figure 1.4, it determines the following discount rate values at each state of nature (figure 1.6).

For example, at the state of nature identified by coordinates $(6, 1)$ in figure 1.5, the discount rate W assumes the highest value 23.1% (figure 1.6). This represents the point of maximum technical risk at the beginning of the development phase, and an uncertain project value in term of TPP. At this stage there is a lot of uncertainty and several future outcomes are possible.

Coordinates $(1, 1)$ in figure 1.5 show the point where the discount rate W assumes the lowest value 8.1% [18]. This amount is higher than the risk-free rate of 3.8% and reflects the low risk profile of the managerial option. Indeed, it represents a point of minimum technical risk

[18]The value is lower than the discount rate of the project after launch (8%) where only market risk is present.

at the end of the development phase, and a high level of project value supported by the TPP. This is now the final phase of development where outcomes are more predictable.

At the point of coordinates $(1, 6)$ the discount rate W assumes a value of 17.1%. It represents a point of minimum technical risk at the end of the development phase but the TPP level implies a low project value[19]. This dynamic of the discount rate reflects the fact that in sequential types of investments, the company goes ahead only if R&D program hits a sufficient threshold value. In less uncertain states of nature, investments are carried ahead on a lower threshold value (Dixit and Pindyck 1994). Each successfully completed stage of the project reduces the technical uncertainty and increases knowledge, experience and insight into the dimensions of the market.

The risk adjusted rate calculation reflects a subjective valuation of a project's risk profile that is determined by the prevailing technical and market conditions. A market approach that derives discount rates from assets traded in the financial market (Rogers 2009) does not hold because, as previously discussed, market replicating assets cannot be found. This supports the argument that a contingent claim analysis approach is not applicable in the pharmaceutical industry.

1.7.2 Peak sales scenarios

The peak sales are the maximum sales a drug reaches once launched on the market. Peak sales generally occur towards the end of a drug's life span, often the year before loss of patent exclusivity. The different values that they can assume along the various paths of the cone of uncertainty are obtained by spanning the binomial tree, starting from the initial node S_0. The value attributed to S_0 is the average value of the peak sales prediction for the specific project[20]. The value is \$320Mio (see figure 1.7) at the beginning of the development process.

The choice of the average peak curve is consistent with the volatility calculation, but also reflects the difficulty of predicting exact peak sales values for a drug that will not be launched for another 6-8 years and whose market potential is still uncertain.

Referring to the calculations performed above in section 1.5.1 where the volatility parameter, based on a specific calculation for the Therapeutic Area Infectious Diseases, amounts to 29% (Appendix 1).

[19]The TTP evolves along the development tree as more information is available and resembles the drug to be marketed in the future. Among others, it covers factors such as indicaton, posology, specific population and ultimately the vision of the brand and the marketplace.

[20]cf. Appendix 1

Based on the volatility measure of 29% and a fraction of time Δt= 1 year, the parameters necessary for the development of the binomial tree are calculated. The choice of $\Delta t = 1$ is dictated by the availability of yearly sales data. Contrary to the financial option setting where a very short time step (dt) is required for accuracy, in a real option settings wider time steps are allowed.

Based on the formulae, the following up and down movements and the correspondent real world probabilities are found:

$u = e^{\sigma\sqrt{\Delta t}} = 1.34$

$d = e^{-\sigma\sqrt{\Delta t}} = 0.75$

$p = \frac{(1+\mu)^{\Delta t}-d}{u-d} = 51\%$

The parameter μ represents the drift of the peak sales forecast. The drift is = 5% and is represented by the "regimen growth rate". This rate is calculated by marketing analysts and represents the predicted growth rate of the segment "antibacterial " over the next 10 years, within the TA of ID. The regimen growth rate therefore accounts for the potential development of an antibacterial drug while taking into consideration market dynamics including competition, the entry of generics and market share evolution.

A closer look at the tree allows the following considerations :

- Extreme values of peak sales (in the upper and lowest nodes) have a very low probability of realization. For example, in figure 1.7, peak sales of $1823 (at the very upper limit) have only a 2% chance of occurring.
- The peak sales growth in expectation is 5%, as constructed by the parameter μ.
- The expected value of peak sales is $429 Mio, calculated as an arithmetic average. For example, the value 429 in the column denoted in step 6 (figure 1.7) is calculated using the development of the binomial $(1 + x)^n$ where $n = 6$. The binomial coefficients are found in the binomial triangle.

The value 429 is = $1823 \cdot P^6 + 6 \cdot 1021 \cdot P^5 \cdot (1-P)^1 + 15 \cdot 572 \cdot P^4 \cdot (1-P)^2 + 20 \cdot 320 \cdot P^3 \cdot (1-P)^3 + 15 \cdot 179 \cdot P^2 \cdot (1-P)^4 + 6 \cdot 100 \cdot P^1 \cdot (1-P)^5 + 56 \cdot (1-P)^6$.

The same value of 429 is calculated as an expected value. This is obtained by calculating the binomial probability of reaching each final node, multiplied by the corresponding final state value. For example the value 1823 is multiplied by the corresponding probability of realization of 0.02 to obtain the probability weighted value of 33. The sum of all the probability

steps	0	1	2	3	4	5	6
Sales	320	428	572	764	1021	1364	**1823**
		239	320	428	572	764	**1021**
Probability P weigthed		336	179	239	320	428	**572**
Growth rate		*5%*	353	134	179	239	320
Geometric mean		320	*5%*	**370**	100	134	**179**
			320	*5%*	**389**	75	**100**
				320	*5%*	**408**	56
					320	*5%*	**429**
						320	*5%*
							320

Up steps	Prob. P of state	Prob. P weigthed
6	0.02	33
5	0.10	106
4	0.25	141
3	0.31	100
2	0.22	40
1	0.08	8
0	0.01	1
Exp.Value		429
drift		5%

Figure 1.7: Binomial tree development of peak sales

Final Values	Up steps	Prob. P of state	Log changes	Prob. Weigthed	(Log changes)^2	(Prob. Weigthed)^2
a)	b)	c)	d)	e)	f)	g)
1823	6	0.02	0.290	0.005	0.084	0.002
1021	5	0.10	0.193	0.020	0.037	0.004
572	4	0.25	0.097	0.024	0.009	0.002
320	3	0.31	0.000	0.000	0.000	0.000
179	2	0.22	-0.097	-0.021	0.009	0.002
100	1	0.08	-0.193	-0.016	0.037	0.003
56	0	0.01	-0.290	-0.004	0.084	0.001
			geometric mean changes	0.75%		**1.41%**
			St.Deviation	29.0%		

Figure 1.8: Probability weighted log changes

weighted values is equal to 429. Comparing the value of 429 with the initial value of 320, by calculating the changes, we find that the growth rate over six years is exactly the drift rate of 5%[21]. The value of 5% is the growth rate of the peak sales, and the arithmetic mean of changes.

Figure 1.8 shows how updates of peak sales have a geometric mean of changes of 0.75% and a standard deviation of 29%, confirming the initial assumption. The log of changes are defined as the log of S_f/S_0, where S_f represent the final values and $S_0 = 320$ the initial value.

The mean is calculated as the sum of the probability weighted log changes (the products of elements of column c multiplied by d). In the specific case the variance of log changes is calculated as $E(X^2) - E(X)^2$, that is $(1.41\% - (0.75\%)^2) \cdot 6$ (where 6 is the number of periods) and leads to a standard deviation of 29%.

1.7.3 The sale curve

The previous section analyzed how peak sales scenarios are modeled. Peak sales following various trajectories are available at the end of the R&D process. Fig 1.7 shows the scenarios dynamics, such that at the end of the development process the possible peak scenarios are identified. From each peak an entire sales curve is calculated following a percentage structure

[21]Notice that by construction the value 320 represents the geometric mean of peak sales realizations at each step.

based on empirical data. For example a peak sales of $1823Mio (see Appendix 2 -eNPV calculation, figure 1.24) is considered appropriate under a very optimistic scenario. The sales curve uptake of the specific drug is such that percentages of 5%, 20% and 51% are considered appropriate for year 1, 2 and 3 after launch, which correspond to years 8, 9 and 10 respectively. The corresponding sales estimates are about $91Mio, $365Mio and $930Mio. The values obtained correspond to expected values under the assumption of μ piecewise constant and changing each year to reflect marketing forecasts. As introduced in section 1.4.2 In year 1 expected sales can be written as:

$$E_0^p[V_1] = V_0 e^{\mu_1^V}$$

$365 = 91e^{\mu_1^V}$ that is $\mu_1^V = 1.39$[22], or a drift of 139% for the first period. This is equivalent to expressing the amount of sales in growth rate terms.

In a recursive way it can be shown that the drift for the second period μ_2^V is 190%.

$$E_0^p[V_2] = V_0 e^{\int_0^2 \mu_s^V ds} = V_0 e^{\mu_1^V + \mu_2^V}$$

$930 = 91e^{\mu_1^V} e^{\mu_2^V}$

$\mu_2^V = ln(\frac{930}{91e^{\mu_1^V}}) = 1.9$

In this way we have shown how the sales curve calculated following a percentage structure based on empirical data can be represented in mathematical terms.

1.7.4 An R&D project – the compound option

As outlined previously, there are two kinds of uncertainties that interrelate and shape the decisional process during the R&D phases. Technical risk relates to production risk and the likelihood of successfully passing the clinical trials of each phase. Market risk relates to the market potential of the drug, and the competitive landscape within which it is being launched.

Assuming that no technical risk is associated with a given project allows practitioners to focus on the market risk component in isolation. Under these conditions, market risk analysis alone will determine the decision to continue or abandon the project. As has been shown, in the pharmaceutical industry this not a realistic assumption. However, for the purposes of understanding the structure of the compound option, it is useful to include it here.

[22]The value of 1.39 is the yield rate

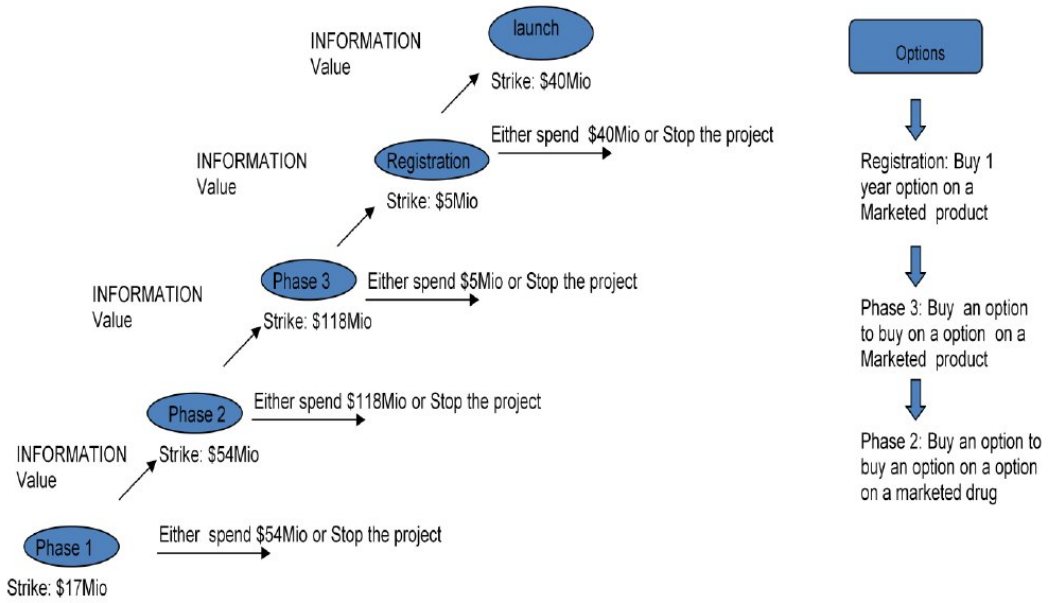

Figure 1.9: Sequential Compound Option

The compound option structure highlights the "crucial decision option", where, in the case of the present example (see figure 1.4), a decision must be made as to whether to spend $40Mio to launch the new product and profit from the free cash flows generated by the sales of the drug on the market, or to 'cut losses' and abandon.

For example, moving back along the decisional process in figure 1.9, a previous decision exists concerning investment in NDA filing. This investment buys a one year option on a marketed product with a strike price of $40Mio and underlies the expected market value of a drug launched one year later. If the option is worth more than $5Mio the firm will choose to continue, if not, it will abandon. Applying the same logic, the $118Mio of the investment in Phase 3 buys an option to buy an option, i.e. the underlying is a one year option on a marketed product. The firm will spend $118Mio on phase 3 only if the option to buy an option on a marketed drug is worth more than $118Mio.

In this way, by the end of the process investors buy options on options in a recursive way, where the learning process on the marketed drug value allows the firm to decide between continuing (buy the successive option) or abandoning the project at each point in the process.

Since there is no technical risk, the probability of successfully moving to the next phase is 100%. In these conditions, the only relevant uncertainty is described along the tree by the differing market value potentials assumed by the drug.

year	1	2	3	4	5	6	
	Ph.1	Ph.2a	Ph.2b	Ph.3	Ph.3 IA	Ph.3	Registration
Dev. Expense	12	28	28	39	39	39	
Prob.of Moving	100%		100%			100%	
NPV Value	143	292	527	868	1342	1970	2769
		92	220	409	684	1054	1534
			60	166	328	550	842
				37	136	273	455
					32	120	238
						36	117
							49

Figure 1.10: Binomial tree with only market risk (Project value NPV)

Based on end nodes values of the peak sales' tree development, the NPV value of the drug (figure 1.10) at the time of launch is calculated. Since the project is assumed to be already launched, the discount rate used is constant (8%).

For instance, $2769Mio represents the NPV of the drug launched under a very optimistic scenario with peak sales of $1823Mio as detailed in Appendix 2.

The evolution of the project value tree allows, at each state, the calculation of the maximum value between the underlying minus the strike or zero to be made. In this way the value of 2769 is maximum [2774-5, 0] where 5 is the NDA filing cost as reported in figure 1.4). Once all NPV values at the terminal nodes are calculated, it is possible to recursively proceed to calculating the project values at each node.

Formulae (1.2) and (1.3) are applied at each node to calculate the project value.

At the end of each development phase the probability of successfully passing the phase must be considered and the project value is obtained by applying formula (1.2). In this simplified case where only market risk is considered, the probability of successfully moving to the next phase is always 100%.

At the beginning of each development phase the company faces a decision point as to whether to continue or not with the development of the project. The project value is calculated by applying formula (1.3).

For example the net value $1342Mio is calculated as:

$$[51\% \cdot 1970 + (1 - 51\%) \cdot 1054]/(1 + 10.6\%) - 39 \cdot (1 - 10\%)$$

where 51% is the real world probability p of an upward movement, $1970Mio and $1054Mio represent respectively the up and down values on the following period (the year) and $39Mio are the ongoing development expenses of the specific development phase (phase 3 IA). The value of 10% is the company marginal tax rate and the value of 10.6% represents the risk adjusted discount rate appropriate for the specific state of nature of the project as calculated in

figure 1.6.

The project value tree (in figure 1.10) shows no states in which the optimal decision is to discontinue development. This is because the expected market value of the drug looks profitable enough to support the development costs at each phase. The abandonment option is worthless because the project generates positive cash flows, even in the most negative states of nature along the tree. To conclude, in only considering market risk, the probability of spending \$40 million to launch the drug is greater than 23% (value which was introduced in section 1.7, figure 1.4). This is the standard cumulative Probability to Approval (P) for a drug in phase 1, and reflects the probability of successfully passing through all previous phases and reaching the market (see figure 1.4). The same is true for all the development expenses, since development costs will only be spent in situations where the NPV at each decisional point (based on what is known about the drug market value) is positive.

While in theory focusing solely on market risk so as to explore the sequential structure of the compound option is useful, it is unrealistic. In reality, the uncertainty of the drug is affected also by technical risk. Technical risk is determined by the inability to guarantee the successful passage of the drug through each phase up to launch. Technical risk has two effects. The first is specific risk which is unrelated to the macroeconomic state of nature. Specific risk is captured in the analysis as an exogenous impact that can occur at the end of each development phase or, like interim analysis, when clinical data becomes available. The second effect is determined by the interrelation of technical risk with market risk and has a continuous impact during the lifespan of the project. It is precisely this second effect that is accounted for in the calculation of the risk adjusted discount rate mentioned previously.

Analysis of the project value tree shown in figure 1.11, calculated by considering both technical and market risk, shows states in which it is optimal to abandon, because the value of the project is negative. These negative values originate from downside scenarios, where peak sales show a low realization. Project value is calculated using formula 1.2. For example the net value of \$1067Mio is calculated as

$$58\%[51\% \cdot 2630 + (1 - 51\%) \cdot 1457]/(1 + 8.1\%) - 39 \cdot (1 - 10\%)$$

where 58% is the probability of successfully moving to Registration phase, 51% is the real world probability p of an upward movement, \$2630Mio and \$1457Mio represent respectively the up and down values on the following period (the year) and \$39Mio are the ongoing development expenses of the specific development phase (phase 3). The value of 10% is the company marginal tax rate and the value of 8.1% represents the risk adjusted discount rate

year	1	2	3	4	5	6	
	Ph.1	Ph.2a	Ph.2b	Ph.3	Ph.3 IA	Ph.3	Registration
Dev. Expense	12	28	28	39	39	39	
Prob.of Moving	66%		64%			58%	
eNPV Value	-1.44	53	145	435	708	1067	2630
		-16	38	183	346	563	1457
			-17	49	150	286	800
				-21	45	134	432
					-12	50	226
						4	110
							46

Figure 1.11: Binomial tree with technical and market risk (Project value eNPV)

year	1	2	3	4	5	6	
	Ph.1	Ph.2a	Ph.2b	Ph.3	Ph.3 IA	Ph.3	Registration
Dev. Expense	12	28	28	39	39	39	
Prob.of Moving	66%		64%			58%	
Value with RO	2.92	53	145	435	708	1067	2630
		0	38	183	346	563	1457
			-12	49	150	286	800
				0	45	134	432
					0	50	226
						4	110
							46

Figure 1.12: Project value with flexibility

appropriate for the specific state of nature of the project as calculated in figure 1.6.

If the option to abandon is omitted from the tree, the final value of the project = -1.44. This would be the same value obtained via a DCF eNPV analysis that captures (by incorporating revenues and costs weighted by their probability of occurrence) only technical risk, while not considering flexibility regarding the market potential of the drug (if we used a constant discount rate along the tree).

The exercise of flexibility implies the potential to discontinue at each decision point. This is represented at the beginning of each phase (year 2 and 4) and at the beginning of the second year of phase 3 (year 5) when the results of the Interim Analysis become available (see figure 1.12). The possibility to discontinue the project allows for the exclusion of the project negative values (see figure 1.12).

As shown in figure 1.11, at the beginning of Phase 2 the project shows a negative value creation of -$16Mio that can be avoided by stopping the project. The same holds true for the beginning of phase 3 in year 4 and at the release of the IA results in year 5. Figure 1.12 indicates that the exercise of flexibility leads to a project value of $2.92Mio. Notice the persistence of negative values generated in year 3 (-$12Mio) due to the technical impossibility to stop the

project in this year.

The difference between the value of the project without flexibility ($-1.44 Mio) and with flexibility ($2.92Mio), represents the value of the sequential compound RO which in this instance is around $4 Mio.

These results support the statement that technical and market risk interact and work together to determine the optimal exercise versus abandonment option. In the pharmaceutical industry, both types of risk need to be considered in tandem in compound option analysis in order to gain an accurate understanding of the whole investment picture.

1.7.5 A further example: the development of a parallel indication

This second example refers to the hypothetical expansion of a parallel indication of the antimicrobial drug currently being developed and analyzed in the first example, which is a topical antibacterial cream used to treat skin infections after injury (Therapeutic Area Infectious Diseases) . The expansion is an option to grow that the company can implement if technology and market conditions are favorable.

Antibacterial (antimicrobial) drugs can be classified on the basis of their biological activity, the effect that they have on microorganisms. There are the bactericidal compounds that kill bacteria, as well as bacteriostatic compounds that slow down or stop bacterial growth. The drug or the NME (new molecular entity) under development in the first example was a topical antibacterial cream used for post-injury skin infections. In contrast, the PIE (parallel indication expansion) of this second example is a topical ointment for eyes which is used in the treatment of bacterial conjunctivitis. The ointment works by preventing the production of proteins necessary for the bacteria to grow and replicate.

The development of the parallel indication (figure 1.15, 1.16) can start either when the underlying antimicrobial cream is in phase 2a, or after 1 year at phase 2b (figure 1.18, 1.19). Starting at phase 2b it means leveraging on the clinical trials performed in phase 2a while losing market potential from the one year delay. Conversely, starting in parallel to phase 2a may mean more development risk, but there is the potential commercial benefit of being one year closer to market.

The value of a deferral option

The indication expansion is first evaluated under both timelines development.

	Time (years)	Costs ($Mio)	PoS
Phase 2a	1	5	64%
Phase 2b	1	8	80%
Phase 3	3	33	58%
NDA filing	1	5	95%
Launch	1	40	100%

Figure 1.13: Development costs and PoS

Decisions are then made regarding the optimal development time and the value of the option to 'wait' is estimated. Finally, an estimation is made of the value of the indication expansion.

The peak sales of the eye drug proposed in the second indication is estimated to reach $70Mio if the molecule starts development in parallel with phase 2a . This estimate falls by about 30%, ($50Mio) due to erosion of market share by competitors, if development starts at phase 2b. The development costs of the second, or parallel, indication (figure 1.13) are relatively lower than the costs of the precursor drug, the topical cream (figure 1.4). This is because all the stability, formulation and toxicity studies have already been performed, and passed, by the precursor drug[23].

In comparing the two options (starting either in phase 2a or 2b), the sunk costs of starting at phase 2b reduce development expenses by $5Mio while the technical PoS (probability of successfully moving to the next phase) increases from 64% to 80% when starting at phase 2b. This reflects a higher chance of the indication successfully passing to phase 3, because by waiting one year the technical risk of phase 2 is partially resolved. The analysis starts by considering the value of the parallel indication under the two timelines of development (in correspondence of phase 2a or 2b of the precursor). Once the optimal development timeline has been identified, the expansion option value is obtained by integrating the value of the parallel indication (the eye ointment) into the real option tree of the precursor indication (the topical cream).

The parallel indication under the first development scenario is assumed to be developed with a timeline in conjunction with phase 2a of the precursor drug. The valuation follows the same steps as in the previous example that presented the value estimation of the precursor drug, the topical antibacterial cream.

[23]Figure 1.13 shows the development costs for the parallel indication: a total of $46Mio ($5Mio+$8Mio+$33Mio) if the molecule starts in parallel with phase 2a; a total of $41Mio ($8Mio+$33Mio) if the molecule starts in parallel with phase 2b.

steps	0	1	2	3	4	5	6
Sales	70	94	125	167	223	298	**399**
		52	70	94	125	167	**223**
			39	52	70	94	**125**
				29	39	52	70
					22	29	**39**
						16	**22**
							12

Figure 1.14: Binomial tree development of peak sales

year	2	3	4	5	6	
	Ph.2 a	Ph.2 b	Ph.3	Ph.3 IA	Ph.3	Registration
Dev.Exp.	5	8	11	11	11	
Prob.of Moving		64%			58%	
eNPV Value	**2.01**	18	71	131	212	547
		-4	20	55	104	290
			-7	15	45	147
				-7	12	66
					-6	21
						-4

Figure 1.15: Project value eNPV

1) Based on peak sales of \$70Mio, volatility of 29% and time steps (Δt) of 1 year, development of the cone of uncertainty begins; reflecting the various possible sales paths' as shown in figure 1.14. The development of the binomial tree is based on factors $u = e^{\sigma\sqrt{\Delta t}} = 1.34$ and $d = e^{-\sigma\sqrt{\Delta t}} = 0.75$.

2) Based on a value μ (the estimated growth rate of peak sales for the parallel indication) of 3% the real world probabilities are calculated using: $p\,real = \frac{(1+\mu)^{\Delta t}-d}{u-d} = 48\%$. The growth of 3% is considered appropriate for the specific eye antibacterial segment (compared to the 5% growth rate of the broader antibacterial market) and is provided by marketing analysts. The calculations develop the eNPV valuation of the project on the market for each sales path. For example, the value of peak sales of 399 (see step 6 of figure 1.14) correspond to an eNPV value of 547. (see Appendix 3- eNPV calculation). The RO value is calculated by working backwards through the market values. Figure 1.15 shows the preliminary eNPV value of the parallel indication amounting to \$2.01 Mio.

Figure 1.16 shows the value of the same project based on the RO approach which includes flexibility. The project is stopped (thus limiting the losses) at registration, at the IA (interim analysis of phase 3) and at the beginning of phase 3. The value of the parallel indication increases to \$2.80Mio.

As for the earlier case study on the precursor drug, the risk adjusted discount rate is used for discounting after registration once the product is launched on the market. As before, it

year	2	3	4	5	6	
	Ph.2 a	Ph.2 b	Ph.3	Ph.3 IA	Ph.3	Registration
Dev. Expense	5	8	11	11	11	
Prob.of Moving		64%			58%	
Value with RO	2.80	18	71	131	212	547
		-2	20	55	104	290
			0	15	45	147
				0	12	66
					-5	21
						0

Figure 1.16: Project value with flexibility

step	0	1	2	3	4	5	6
Sales	50	67	89	119	159	213	**285**
		37	50	67	89	119	**159**
			28	37	50	67	**89**
				21	28	37	50
					16	21	**28**
						12	**16**
							9

Figure 1.17: Binomial tree development of peak sales

remains constant at 8% and represents the company risk adjusted discount rate. Conversely, the discount rate used when working backwards through the tree from registration to phase 2a is not constant. Instead it changes to account for the different levels of risk along the tree. The calculations, illustrated in Appendix 4, are based on the same parameters as those used in the first example, the precursor indication (section 1.7.1), but are further adjusted to account for the fact that the development process starts in conjunction with phase 2a.

The development team evaluates a second scenario. Here the parallel indication is developed one year later, that is in parallel with phase 2b of the precursor.

Figures 1.17 and 1.18 show the steps taken for evaluating the parallel indication, with figure 1.17 representing the development of the binomial tree of peak sales. Due to competition, the one year delay in market launch results in a substantial decrease in the average peak sales, reduced to \$50Mio. Based on the same up and down factors calculated previously, $u = e^{\sigma\sqrt{\Delta t}} = 1.34$ and $d = e^{-\sigma\sqrt{\Delta t}} = 0.75$ the cone of uncertainty is developed.

As previously mentioned, the one year delay allows leverage on the clinical results of phase 2a and reduces the development expenses, or sunk costs, by \$5Mio. The technical PoS of passing to phase 3 is 80%, reflecting the partial resolution of uncertainty from successful completion of phase 2a.

It has already been shown that the discounted rate in the parallel indication constantly change to reflect different levels of risk, this is described in the present example (see Appendix

year	3	4	5	6	
	Ph.2 b	Ph.3	Ph.3 IA	Ph.3	Registration
Dev. Expense	8	11	11	11	
Prob.of Moving	80%			58%	
eNPV value	8.87	38	81	140	380
		2	27	63	197
			-1	21	94
				-2	37
					5

Figure 1.18: Project value eNPV

year	3	4	5	6	
	Ph.2 b	Ph.3	Ph.3 IA	Ph.3	Registration
Dev. Expense	8	11	11	11	
Prob.of Moving	80%			58%	
Value with RO	9.08	38	81	140	380
		2	27	63	197
			0	21	94
				-2	37
					5

Figure 1.19: Project value with flexibility

5) where the risk adjusted rate in year three is lower than the correspondent rate for phase 2a (16.1% versus 16.7%, see Appendix 4). This is explained by the 80% PoS of successfully moving to phase 3. This makes the cumulative Probability to Approval, used in the discount rate calculations, increase from 35% to 44%[24] which reflects a reduced risk of technical failure and thus a lower risk adjusted discount rate.

Figure 1.18 reports the calculations used to estimate the value of the PIE under the assumption that the eye ointment is developed one year later, which is when the antibacterial cream is already in phase 2b. Also in this situation there is a state of nature in which it is convenient to discontinue at phase 3 when Interim analysis results are disclosed.

As shown in figure 1.19 the value of the PIE with flexibility, that is with the RO approach, becomes $9.08Mio.

A high PIE value informs management to start the development in parallel of phase 2b of the precursor indication. The difference between the two values of the parallel indications ($ 9.08Mio - $2.80Mio = $6.3 Mio) represents the value of the option to wait.

The optimal timing of project execution can occur when technical uncertainty dominates

[24]With reference to figure 1.4 the cumulative Probability to Approval (P) of the compound starting in phase 2a is given by $64\% \cdot 58\% \cdot 95\% = 35\%$, which becomes $80\% \cdot 58\% \cdot 95\% = 44\%$ when starting in phase 2b.

Sales ($Mio)	$45	$44	$43	$42	$41	$40	Phase 2a
eNPV	4.58	3.73	2.87	2.01	1.15	0.3	2.01
RO	5.31	4.81	4.24	3.66	3.09	2.51	2.8

Figure 1.20: Sensitivity on the peak sales for the PIE in correspondence of phase 2b

market uncertainty, making waiting the best strategy. By deferring development of the PIE for 1 year, management will have a better knowledge of the technical process, thus reducing technical risk. The value of this information is embedded in the option to wait. Despite a reduction of about 30%, leading to peak sales of $50Mio as opposite to $70Mio, as shown above, the phase 2b development is the preferred strategy because there is less potential risk of larger losses should a lack of technical knowledge result in failure. At this point it is useful to determine what the peak sales critical threshold for deferring the PIE development process is. Figure 1.20 illustrates how if peak sales fall below $40Mio then the preferred option is to develop the PIE when the precursor antibacterial cream is in phase 2a. Indeed, at this level of peak sales the value of the PIE under RO analysis would be $2.8 for phase 2a timeline versus $2.51 of the phase 2b timeline. The value of the option to wait is highly dependent on the competitive setting. In a highly competitive environment such the pharmaceutical industry the decrease in profitability following the loss in market share, can completely destroy the option to wait.

The value of the expansion option

To understand the value of the expansion option for the precursor drug it is important to integrate the value of the parallel indications into the real option tree of the precursor (the topical antibacterial cream). This is shown in figure 1.21 where the values in conjunction with phase 2b include the expansion option. For example the project value of 154 at the end of phase 2b is obtained as: $64\% \cdot [(51\% \cdot 435) + (1 - 51\%) \cdot 183] \cdot (1/16.7\%) - 28 \cdot (1 - 10\%) + 9.08$, where:

- 64% is the PoS of successfully moving to phase 3
- 51% = real world probability
- $435Mio and $183Mio represent respectively the up and down values on the next period
- $28Mio are the development expenses
- 10%= company marginal tax rate

year	1	2	3	4	5	6	
	Ph.1	Ph.2a	Ph.2b	Ph.3	Ph.3 IA	Ph.3	Registration
Dev. Expense	12	28	28	39	39	39	
Prob.of Moving	66%		64%			58%	
Value with RO	4.90	60	154	435	708	1067	2630
		0	47	183	346	563	1457
			-3	49	150	286	800
				0	45	134	432
					0	50	226
						4	110
							46

Figure 1.21: Project value with flexibility

- $9.08Mio is the value of the parallel indication integrated in the option tree of the precursor indication (the topical cream)
- 16.7% represents the risk adjusted discount rate appropriate for the specific state of nature of the project as calculated in figure 1.6.

As before, the project is stopped (thus limiting the losses) , at the IA (interim analysis of phase 3) and at the beginning of phase 3 and phase 2a.

The value of the project with flexibility, that is based on the RO approach, embedding the expansion option is $4.90Mio. The expansion (growth) option value can be quantified as the difference between the value of the precursor project with and without expansion. That is $4.90Mio and $2.92Mio, giving a value of the expansion option of about $2Mio.

1.8 Conclusions

This chapter introduced RO theory and verified the practical applications of this model to the pharmaceutical industry. Having analyzed the suitability of the RO model in the investment decision process, the present study critically analyzed the differences in the literature regarding the applicability of the model, and found the RO approach based on real world probabilities (p) and risk adjusted discount rates as being more suited to pharmaceutical business opportunities since assumptions such as the replicating portfolio and the contingent claim are not applicable.

Having identified and analyzed the two main types of uncertainty present in the pharmaceutical business, market and technical, the present study supports the theories of practitioners such as Shokley (2007) and Berk et al. (2004) who argue that market and technical risk are best

addressed in an integrated manner. Market value and a project's profit forecast are constantly monitored during the development phase. It is not uncommon for drug development to cease because the market potential is considered inadequate. In turn, due to the nature of the pharmaceutical industry where a substantial proportion of risk is associated with the successful passage of a drug through various stages in development, this study challenges authors such as Kodukula and Papudesku (2006) who suggest that these forms of risk can be addressed independently.

How these two forms of risk are then integrated into calculations of risk adjusted discount rates appropriate for the various state of nature of the development cone of uncertainty is next addressed. The rates are used to calculate the values of the project.

An illustrative example on the R&D process was presented using the example of the infectious diseases treatment area. This example was used to illustrate how the RO model can provide an adequate analytical framework to analyze value creation within an R&D process. Specifically, the valuation of a compound sequential option, of a waiting option and an expansion option were explored.

With respect to the valuation of the waiting option, the example shows that in a competitive environment the option to wait can easily lose its value. In a highly competitive environment such the pharmaceutical industry the decrease in profitability following the loss in first mover advantage, can wipe out the option to wait.

This chapter has shown how the RO model offers a convenient analytical tool that conforms to the environmental idiosyncrasies of the pharmaceutical industry. Nevertheless, the accuracy within which parameters are estimated is crucial. One of the key parameters that can heavily impact on the results of the analysis is volatility. In this context two kind of volatility parameters are introduced: the volatility of peak sales predictions "σ" and the volatility of the entire sales curve "σ^V". The volatility of peak sales predictions "σ" is calculated based on data from real portfolios. Conversely research on the volatility of the entire sales curve "σ^V" is performed using managers' assumptions based on their market knowledge. The results of these calculations highlight not only the importance of accuracy in the data selection phase, but also of focusing the calculation to the specific TA of interest so as to obtain a correct estimation of the model parameters.

This study argues that the RO approach is superior to the traditional NPV and eNPV due to their inability to incorporate flexibility into the valuation process. Evidence of this is found in projects that are continued despite displaying either a negative NPV, or financial market

reactions that are positive to unexpected increases in R&D budgets. This apparent disconnect between the static traditional NPV with the financial markets movements, and managers intuition is reconciled using the RO approach. RO offers the analytical framework within which to quantify the intuition behind true strategic valuations of a project, clearly recognized by financial markets.

One characteristic of the RO application is that it can only be applied to situations that are structured like options. That is, projects that can be strategically redesigned if conditions become no longer profitable. RO allow to implement what Van Putten and MacMillan (2004) deem essential: "no valuation method would save a company that does not pull out quickly and redeploy funds in promising projects".

PEAK=Pk	Mean	Z = Pk/mean curve		Changes	Ln(Changes)
789	547	1.4	1.4		
731	411	1.8	1.8	1.23	0.21
876	551	1.6	1.6	0.89	-0.11
1'629	1'137	1.4	1.4	0.90	-0.10
1'060	763	1.4	1.4	0.97	-0.03
1'017	**682**	**1.49**	1.5	1.12	0.11
			2.0	1.31	0.27
			1.7	0.84	-0.18
353	228	1.5	1.6	0.93	-0.07
116	57	2.0	1.5	0.97	-0.03
281	165	1.7	1.6	1.04	0.04
287	181	1.6	1.6	1.00	0.00
565	437	1.5	1.6	0.99	-0.01
320	**214**	**1.60**	1.7	1.09	0.08
			1.6	0.90	-0.10
1'425	890	1.6	1.8	1.16	0.15
1'370	858	1.6	2.1	1.15	0.14
1'172	739	1.6	2.1	0.99	-0.01
1'172	681	1.7	1.3	0.63	-0.46
1'172	754	1.6	2.4	1.87	0.62
1'262	**784**	**1.61**	2.4	0.98	-0.02
			1.9	0.78	-0.24
			1.3	0.69	-0.37
805	446	1.8	1.2	0.91	-0.10
554	266	2.1	1.2	1.00	0.00
359	175	2.1	1.6	1.36	0.30
216	167	1.3	1.4	0.90	-0.11
483	**263**	**1.84**	1.9	1.34	0.29
			1.9	0.99	-0.006
185	76	2.4	1.7	0.89	-0.114
108	46	2.4	2.0	1.17	0.157
55	30	1.9	2.3	1.17	0.156
79	61	1.3	1.8	0.78	-0.251
131	112	1.2	2.2	1.21	0.194
154	132	1.2	2.3	1.05	0.049
119	**76**	**1.56**	2.2	0.98	-0.021
			2.5	1.09	0.091
824	519	1.6	2.4	1.00	-0.003
1'645	1'157	1.4	1.6	0.64	-0.451
1'640	861	1.9	2.1	1.35	0.303
1'640	867	1.9	2.7	1.27	0.239
1'437	**851**	**1.69**	2.0	0.73	-0.314
			2.2	1.11	0.108
825	418	2.0	2.2	0.99	-0.011
627	271	2.3	1.6	0.76	-0.281
627	349	1.8	1.6	0.97	-0.032
627	287	2.2	1.6	0.99	-0.014
615	268	2.3	1.6	1.04	0.035
644	287	2.2	1.6	0.97	-0.026
683	278	2.5	1.6	1.04	0.037
693	283	**2.4**	1.6	0.99	-0.011
272	174	1.6	1.6	0.98	-0.021
322	153	2.1	1.6	1.00	0.000
348	130	2.7	1.9	1.18	0.169
347	177	2.0	1.6	0.83	-0.182
313	144	2.2	1.6	1.03	0.031
534	**248**	**2.2**	1.6	1.01	0.010
			1.6	0.99	-0.011

Figure 1.22: Appendix 1-volatility calculation

514	315	1.6	1.6	1.00	-0.004
1'281	812	1.6	1.6	1.00	0.004
775	498	1.6	1.6	1.00	0.005
602	374	1.6	1.6	0.97	-0.032
538	343	1.6	1.6	1.04	0.039
538	330	1.6	1.6	0.96	-0.038
602	374	1.6	1.6	1.03	0.027
1'525	967	1.6	1.9	1.20	0.178
1'342	851	1.6	1.6	0.85	-0.167
812	435	1.9	1.9	1.15	0.139
812	522	1.6	1.8	0.98	-0.025
849	**529**	**1.6**	1.8	0.98	-0.016
			2.1	1.18	0.169
428	264	1.6	1.9	0.88	-0.128
915	571	1.6	1.7	0.91	-0.096
497	311	1.6	1.7	0.99	-0.008
915	571	1.6	1.8	1.05	0.050
418	260	1.6	1.7	0.97	-0.026
429	275	1.6	1.7	1.00	-0.004
428	264	1.6	1.9	1.10	0.091
418	268	1.6	1.9	1.01	0.014
915	571	1.6	1.6	0.86	-0.149
497	259	1.9	1.9	1.16	0.145
586	**361**	**1.6**	1.9	1.02	0.015
			1.9	0.99	-0.007
485	260	1.9	2.0	1.02	0.023
534	294	1.8	1.8	0.94	-0.057
640	358	1.8	2.0	1.07	0.064
336	159	2.1	2.0	0.99	-0.006
499	**267**	**1.9**	2.1	1.08	0.081
			2.0	0.94	-0.063
461	272	1.7	2.2	1.08	0.081
403	240	1.7	1.9	0.88	-0.134
680	385	1.8	1.8	0.97	-0.032
515	**299**	**1.7**	1.9	1.05	0.046
			1.8	0.95	-0.046
1'199	699	1.7	2.0	1.07	0.065
1'143	609	1.9	1.9	0.99	-0.006
1'194	627	1.9	1.8	0.93	-0.071
790	482	1.6	1.5	0.83	-0.186
1'137	600	1.9	1.4	0.93	-0.071
1'130	587	1.9	1.5	1.07	0.067
722	378	1.9	1.4	0.91	-0.093
696	356	2.0	1.6	1.19	0.177
1'001	**542**	**1.8**	1.5	0.95	-0.053
			1.6	1.02	0.019
758	385	2.0			
1'520	777	2.0		0.02	variance
1'632	769	2.1			
1'383	694	2.0		15%	
984	456	2.2		29%	
1'280	677	1.9	SDperiodic returns (sales updated 3.5 times a year)		
1'460	798	1.8			
2'696	1'406	1.9			
2'775	1'516	1.8			
3'000	1'536	2.0			
1'749	**901**	**1.9**			
866	479	1.8			
341	227	1.5			
420	300	1.4			
250	167	1.5			
272	199	1.4			
708	435	1.6			
708	459	1.5			
509	**324**	**1.6**			

Figure 1.23: Appendix 1-continued

Operating profit	49%	Mark exp.	15%	Sales	1823	
Marginal Tax rate	10%	WACC	8%			

	Ph.1	Ph.2	Ph.2	Ph.3	Ph.3	Ph.3	Registratior	Launch	Market 1	Market 2
year							7	8	9	10
sales curve							0%	5%	20%	51%
peak sales							1823	1823	1823	1823
Revenues							0	91	365	930
Gross margin							0	45	179	456
R&D expenses										
Launch expenses							15	15	15	
Tax							2	-3	-16	-46
FCF							-14	27	147	410
Probability of Spending							100%	100%	100%	100%
FCF probabilized							-14	27	147	410
FCF discounted							-14	25	125	322

	Market 3	Market 4	Market 5	Market 6	Market 7	Peak	Market 9	Market 10	Market 11	Market 12
year	11	12	13	14	15	16	17	18	19	20
sales curve	65%	85%	90%	95%	98%	100%	95%	75%	50%	25%
peak sales	1823	1823	1823	1823	1823	1823	1823	1823	1823	1823
Revenues	1185	1550	1641	1732	1787	1823	1732	1367	912	456
Gross margin	581	759	804	849	875	893	849	670	447	223
R&D expenses										
Marketing exp.	178	232	246	260	268	273	260	205	137	68
Tax	-40	-53	-56	-59	-61	-62	-59	-46	-31	-15
FCF	363	474	502	530	547	558	530	418	279	139
Probability of Spending	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%
FCF probabilized	363	474	502	530	547	558	530	418	279	139
FCF discounted	263	317	309	301	287	270	237	172	106	49
Project NPV	2769									

Figure 1.24: Appendix 2-NPV calculation

Operating profit	49%	Mark exp.	15%	Sales	399
Marginal Tax rate	10%	WACC	8%		

	Ph.1	Ph.2	Ph.2	Ph.3	Ph.3	Ph.3	Registration	Launch	Market 1	Market 2
year							7	8	9	10
sales curve							0%	5%	20%	51%
peak sales							399	399	399	399
Revenues							0	20	80	203
Gross margin							0	10	39	100
R&D expenses										
Launch expenses							15	15	15	
Tax							2	1	-2	-10
FCF							-14	-5	22	90
Probability of Spending							100%	95%	95%	95%
FCF probabilized							-14	-4	21	85
FCF discounted							-14	-4	18	67

	Market 3	Market 4	Market 5	Market 6	Market 7	Peak	Market 9	Market 10	Market 11	Market 12
year	11	12	13	14	15	16	17	18	19	20
sales curve	65%	85%	90%	95%	98%	100%	95%	75%	50%	25%
peak sales	399	399	399	399	399	399	399	399	399	399
Revenues	259	339	359	379	391	399	379	299	199	100
Gross margin	127	166	176	186	192	195	186	147	98	49
R&D expenses										
Marketing exp.	39	51	54	57	59	60	57	45	30	15
Tax	-9	-12	-12	-13	-13	-14	-13	-10	-7	-3
FCF	79	104	110	116	120	122	116	92	61	31
Probability of Spending	95%	95%	95%	95%	95%	95%	95%	95%	95%	95%
FCF probabilized	75	99	104	110	114	116	110	87	58	29
FCF discounted	55	66	64	63	60	56	49	36	22	10
Project eNPV	547									

Figure 1.25: Appendix 3-eNPV calculation

year	2	3	4	5	6
discount rate	19.2%	16.7%	13.1%	10.6%	8.1%
		18.5%	14.9%	12.4%	9.9%
			16.7%	14.2%	11.7%
				16.0%	13.5%
					15.3%

Figure 1.26: Appendix 4-WACC structure along the tree – Parallel indication starting at phase 2a

year	3	4	5	6
discount rate	16.1%	13.1%	10.6%	8.1%
		14.9%	12.4%	9.9%
			14.2%	11.7%
				13.5%

Figure 1.27: Appendix 5-WACC structure along the tree – Parallel indication starting at phase 2b

Chapter 2

A strategic framework for R&D decisions

2.1 Investments under uncertainty and competition

The analysis of pharmaceutical investments has so far highlighted three main shared features: real world investment projects are mainly irreversible, uncertain and can be strategically postponed (Dixit and Pindyck 1994).

An investment is considered irreversible when a project's costs are not recoverable, that is they are sunk costs. In the pharmaceutical industry, the majority of R&D costs represent irreversible investments with effects in the long term period. For example, development costs for the study of a specific molecule are project specific and thus not recoverable. Also marketing and selling expenses of a specific project, once committed, can rarely be recovered or employed for other projects.

Uncertainty is a common feature of all pharmaceutical projects and comes in two forms. Technical uncertainty relates to the probability of successfully launching onto the market, while economic uncertainty relates to market potentialities.

A project's future cash flow, and ultimately its value, is driven by factors that evolve stochastically such as pricing, volume and costs. Deferral decisions within a development project have strategic implications. For example, by postponing an investment decision a company may acquire further information on relevant variables like market conditions, or pricing dynamics. A decision can be postponed when a company has an option to wait. In doing so, it is able to reduce the downside risk by not investing when market conditions are un-

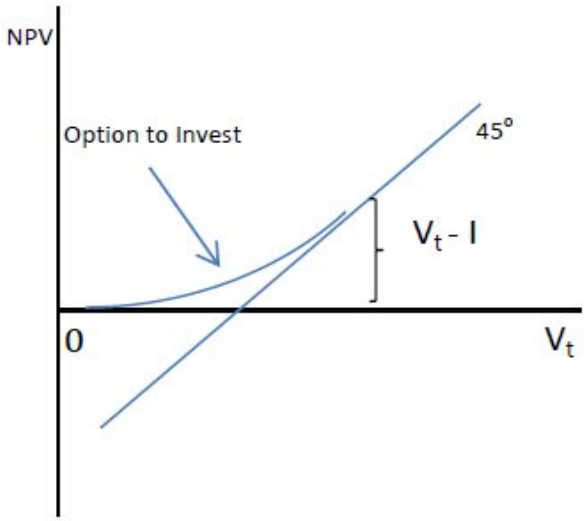

Figure 2.1: Analogy of a deferral project and a call option

favourable, while simultaneously taking advantage of upward opportunities such as positive market trends or a boost in the demand. Time is a valuable parameter to be considered in the decision of option exercise; the possibility to defer allows time to gain a better understanding of future trends which in turn may avoid costly errors during economic downturns. (Kester 1984).

This is analogous to a call option on a dividend paying stock (Smit and Ankum 1993) where the dividend is represented by a project's lost cash flow resulting from the deferral. (see figure 2.1)

As previously discussed in chapter 1, the NPV methodology disregards the main features of a real world investment project. In fact, the underlying assumption of NPV is that either projects are reversible[1], or those that are irreversible are assumed to be "now or never" opportunities without any flexibility to initiate the project in the future. Given these limitations, the NPV method is inappropriate for most pharmaceutical R&D projects. The theory is that

[1]Reversible projects can be undone and the investment costs recuperated in case of negative future scenarios

pharmaceutical projects are subject to uncertainty which evolves according to the stochastic dynamics of the value drivers and embed options. Optimal investment decision must be based on those expected cash flows that exceed the investment cost by a positive amount therefore representing the value at maturity of the embedded options. In reality, when a company decides to take on an irreversible investment it makes a commitment and gives up the option to defer (Leahy 1993). In failing to capture a company's right to abandon or defer an investment, the NPV rule therefore tends to undervalue investments.

The real option approach, in contrast, incorporates the main assumptions of uncertainty, irreversibility and the flexibility of waiting. This methodology therefore more closely adheres to market reality.

A limitation of option valuation is that it focuses on the single company without accounting for the effects of competitive strategic interactions on a firm's decision-making processes. The previous example that described a deferral project and the exclusive right to invest provided by a call option on a dividend paying stock, refers solely to projects in monopoly conditions. Under the real option context, companies are competing only against nature (to reflect the stochastic evolution of market variables), without accounting for any strategic considerations (Boyer, Gravel and Lasserre, 2004).

Game theory provides a richer framework which incorporates real world investment complexities and takes into consideration firms' competitive interactions. By combining options probability theory with game theory, also called option games as defined by Lambrecht and Perraudin (1994), a firm's strategic decisions are taken against both nature and competition. Option games assume a different perspective by capturing competitive implications that might reverse decisions that were previously considered optimal. For example, the option to wait, captured by a real option approach, can lose part of its value when considered from a competitive perspective. There is a tradeoff between the flexibility gained by delaying an investment, and the strategic value of an early move. By being the first on the market the company gains a first mover advantage that defines its strategic positioning. This is particularly relevant in the pharmaceutical industry where a competitive advantage is paramount.

R&D opportunities are available to many companies, but in the pharmaceutical sector only one firm can make a new discovery that when adequately patented will ensure a temporary monopoly rent. Companies therefore engage in patent races to capture market opportunities and block competition from entering the market. In these cases an early commitment kills the option to wait but improves the strategic position of the leader company.

2.2 Competition in the pharmaceutical industry

The pharmaceutical industry is made up of both large multinational companies alongside smaller companies, all involved in the process of researching, producing and commercializing drugs.

The sector is characterized by high levels of innovation based on advancing technology in a largely uncertain environment. For pharmaceutical companies, the most critical issue is to maintain a pipeline that continuously develops new and innovative drugs, thus allowing the company to grow. This is even more significant when existing brand name drugs reach the end of their patent, a time when many companies suffer a dramatic consequential drop in sales.

As stated by D. Vasella Chairman of Novartis: "We are facing real challenges. Patent expiries have lead to revenue losses and our success now depends on our capability to replace lost revenues with new value-adding patented products" (Vasella 2011).

In order to defend the worth of future growth options, a strategic decision to accelerate projects with uncertain profit potential, may be made. Such an approach avoids pre-emption from competition and the erosion of the value of future growth opportunities.

Unlike other large scale industries, competition within the pharmaceutical industry differs due to the comparative uniqueness of its process and timing of new products development. The following features are unique to the pharmaceutical business:

- the R&D process leading to new drugs is highly uncertain. The drug research process is uncertain , and there is no guarantee of a positive outcome with only 1 in 10,000 screened compounds successfully making it to market. (Van Cauter 2010)

- the discovery process is time consuming (in the range of 8-10 years) and numerous challenges in terms of efficacy, safety, and quality must be overcome before any one indication can be commercialized .

- there are high costs in the range of $500Mio-$800Mio associated with the process of drug development against a backdrop of uncertain results.

- there are numerous unique restrictive and changing regulations within the pharmaceutical industry concerning development, production and sales on the market that add uncertainty to the whole process

- Finally, pharmaceutical industry is a big global business, resulting in a highly competitive market environment.

Competition is played out both within therapeutic areas, and between products. Each drug has its own set of competitors (Spilker 1989). The level of competition depends on the demand within specific therapeutic areas. For example, within the neuroscience therapeutic area, competition is high due to the ubiquitous nature of the disease and the potential for high margins. In contrast, therapeutic areas such as neglected diseases (e.g. leishmaniose disease), where demand is less, competition is reduced. A crucial factor in determining competition comes from the order that different compounds enter a new market . The first drug to reach the market for a new therapeutic class normally gains and retains the largest market share, so reaching the market as rapidly as possible with an effective and safe drug becomes crucial. This concept follows the theory of *negative externalities* where returns in the monopoly state exceed those in a duopoly state so that the entry of the follower reduces the profit flow of the first entrant.

The majority of new drugs are therefore successfully developed by a small group of large multinational firms that can consistently afford to allocate around 15%-20% of their profit into R&D activities.

The competition dynamics are mostly non co-operative, forcing companies to engage in *patent races*. When a leader successfully discovers, develops and launches a new drug, followers start producing similar versions of the product in the same therapeutic class, a process known as "me too". Me too drugs have characteristics of differentiation (in various degree) in term of safety or efficacy, as well as containing other attributes perceived as being important by physicians and patients.

This differentiation leads to patent protection and sometimes the acceptance of a higher price by the Patent Authority. The patent system (which is differently regulated in each country) protects newly discovered product or process from being imitated. Patent protection is a way of supporting the investigation and innovation of new drugs. Without the protection represented by patent monopolies, any industry player could copy the drug resulting in inadequate return for the risky, costly and time consuming R&D processes for the leader company.

A patent granted by the HA establishes the exclusive right to use the drug product or process to the inventor who then benefits from a monopolistic rent spanning over 20 years. Since filing for a patent is done during the early phases of development, the patent protection period is thus reduced by the amount of time required to finalize the product and launch it

onto the market.

The main implications of the patent race on the competitive situation are that the leader benefits from a monopoly rent only until a competitor launches its me too version as a close substitute. Example of me too drugs is represented by entire range of the beta blockers that reached the market after the original breakthrough drug Propanol (discovered by ICI Pharmaceutical in the 60ties and used for heart disease treatment). The late comers to markets version like Ranitidine, Cimetidine or Famotidine showed advantages in term of better efficacy, cardioselectivity and safety (Murti 2008).

This changes the competitive landscape by introducing more players onto the market resulting in price adjustments which follow according to a Bertrand differentiated model[2] (Polak 2007). This is because latecomers to market generally have better efficacy and/or safety characteristics, as recognized by the HA, resulting in the attribution of a higher price. Customers, in this case patients and doctors, care about a products' differentiation characteristics.

A further change in competition occurs when generic, or biologically equivalent, drugs enter the market on expiration of the leader's patent.

An article of Bartholow (2011), reports that after patent expiration, the demand for brand name medicines declines by more than 80% due to generic alternatives within 6 months. Generic competition triggers heavy reductions in pricing relative to the brand name. A study of IMS (Intercontinental Marketing Service) retails sales that compares brand names and generics sold in USA between 1999 to 2004 showed that the average relative price of generic drugs is reduced to nearly half the original brand name price following the entry of a second generic manufacturer. In the case of entry of many generic manufacturers, the average generic price falls to about 20% of the branded drug (FDA-US Food and Drug Administration, 2005).

While a reduction in the price may seem more attractive to the consumer, the perception of patients and physicians of a brand is often a greater determinant of whether a market share is lost to generic substitutions. Given the importance of drugs for patients health the demand for drugs product is inelastic and in various degrees less affected by a changes in pricing as many physicians and patients could be willing to spend more on a known and trusted brand. For generic entries to successfully replace prescription drugs that already offer a specific therapeutic advantage they must not only have a more attractive price, but also offer a specific therapeutic benefit (Matraves 1999). The situation is reversed from the point of view of reim-

[2]The model, called the linear-city differentiated product model, changes the assumption of the Bertrand model of identical products by considering differentiated products. The linear distance measures aspects of product characteristics that define the product specific differentiation.

bursement authorities (e.g. health insurance) that strongly enforce the use of generics.

2.2.1 Competition under a game theory approach

A game theory perspective is particularly suitable for analysing investment projects in innovative sectors, like pharmaceuticals, where the R&D process is long, expensive and highly uncertain. Smit and Trigeorgis (2004) highlight the importance for such industries to make preliminary R&D investments so as to ensure the possibility of capturing future growth opportunities. The fact that R&D investment opportunities are available to several companies make the definition of optimal exercise strategy possible only in consideration of the interactions with competitors' option holders' (Villani 2008). In game theory, the dynamics of competition are investigated so as to gain a better understanding of the strategic interactions between competing companies. Interdependencies among firms imply a two way process where one firm's strategic decision must also consider the actions and reactions of other players, and vice versa. Mason and Weeds (2001) identify "leader inefficiencies", where each player ignores the investment effects of other agents, and "follower inefficiencies" where the follower does not consider the impact of its action on the leader. As stated by Judy Lewent CFO at Merck: "Game theory forces you to see a business situation over many periods from two perspectives: yours and your competitor's" (Nichols 1994).

In the primary phases of a patent race a "winner takes all" philosophy is adopted where the leader company benefits from a first mover advantage in a monopolistic market . It is important to note however that the designation of the leader position can be ambiguous until the end. The uncertain nature and the lengthy times scale of pharmaceutical R&D processes are such that the follower can leapfrog and bypass the leader company in the innovation process, thus ensuring itself the patent and first to market position.

A first mover advantage is theoretically analogous to the game battle of the sexes. For example, two friends want to spend an evening together and they can go either to the theater (ballet) or to the stadium. The man prefers the stadium, the woman the theater, but both are willing compromise on their choice rather than staying in alone. The payoff matrix in normal form is the following, as per figure 2.2.

The individual who moves first gains a first mover advantage (Rasmusen 2007). In this example, if the man buys the stadium ticket in advance, the woman is essentially backed into going to the stadium, and vice versa if the woman moves first by buying ballet tickets in ad-

		Woman	
		Stadium	Ballet
Man	Stadium	**2,1**	0,0
	Ballet	0,0	**1,2**

Figure 2.2: The Battle of Sexes

vance. The purchase of the ticket ensures a commitment, thus influencing the other partner's choice by essentially "forcing their hand". In the pharmaceutical industry, this dynamic is played out in a similar way when a follower enters the market, resulting in the development of a "leader and follower" dynamic. The leader "makes the first move" in discovering a product while the follower benefits from information spillover effect or "information-revelation" (Villani 2008), making use of the leader's R&D and marketing activities. This configures the phenomenon of a second mover advantage where the follower achieves an incremental benefit (positive externalities) by being second in the competition. The follower will engage in further research, on top of that already achieved by the leader, in order to come to the market with an adequately differentiated me too drug within the same therapeutic area. This strategic positioning alongside marketing activity become important aspects to the follower when solidifying its niche in the market. In this respect, the followers marketing activities can be simply focused on offering information regarding the characteristics and benefit of the drug, or be more aggressive in order to persuade patients away from competing therapies (Snyder and King 2007).

The patent race and the preemption interaction in a real option context

The dynamics of patent race competition in pharmaceutical allows for the coexistence of both a first and second mover advantage. This has consequences in terms of real options. A patent race assumes that all the players hold an R&D option of a specific drug under development. The first company to make the drug discovery obtains the patent which subsequently entitles them to exclusive rights to commercialize the drug.

During a patent race each player has an incentive to become the leader so they aim to invest sooner so as to pre-empt other competitors from entering the market and gain a mo-

nopolistic position. This works against the option to wait which encourages waiting until the development option is deeply "in the money". That is when the value of the potential drug exceeds the R&D costs by a large option premium. Under competition conditions, the fear of pre-emption forces a player to start the development process (after successful research). In extreme cases of perfect competition, the value of waiting, as advocated by real options, is therefore completely destroyed and the investment project loses its flexibility factor, making the traditional NPV rule more appropriate (Grenadier 2000).

The intuition behind the pre-emption game has been theorized by Fudenberg and Tirole (1985) who explain it in terms of rent equalization. Considering a duopoly, each firm wants to becomes the leader by investing at a certain time T^*. This is because the first to enter the market benefits from a first mover advantage and subsequently enjoys a higher profit. The followers response is to attempt to pre-empt by investing at a slightly earlier time $T^* - \epsilon$, which will in turn trigger other players to invest at $T^* - 2\epsilon$. In theory the game continues until the point when the leader invests, at which point the leader and the follower are faced with the same expected values in an equilibrium that shows rent equalization.

Once the patent race is over, and a leader designated, the followers can take advantage of their position by further exploring the development of the me too version by exploiting some of the leader's existing knowledge and research. The flexibility to wait and availability of information externalities work in favour of the real option value which is enhanced by such a strategic move.

Nevertheless, what is important to consider is the rapidity and the strength of impact of the follower. A complete analysis of these dynamics is presented by Weeds (2006). Weeds highlights the fact that if the follower's reaction is rapid and aggressive, the leader may prefer to wait; losing the possibility of a first mover advantage that would be rapidly jeopardized by a harmful competitor. In contrast, when the reaction of the follower is slow and less impactful, the leader is prone to accelerate its investment so as to preempt the follower. Cottrell and Sick (2002) suggest that companies should compare the benefits of a first mover advantage with losses determined by the waiting option. If the first mover advantage is deemed the dominant strategy, then market entry must be pursued aggressively.

2.3 Game theory: basic concepts

The integration of game theory in the real option setting allows a better understanding of real world projects strategic value. The option game approach permits to move from a project investment appraisal in a monopolist perspective typical of the real option approach to a project valuation within a competitive strategic setting. In the first case we refer to the R&D investments models called "decision theoretic models" that analyze investment decision in isolation. The latter case is reflected in the "game theoretic models" that take into consideration strategic interactions with rival companies (Huisman 2001). Before analyzing option games in further detail, some basic concepts of game theory are provided in the rest of the section.

The fundamental elements that define a game are: the *players*, the *strategies* and the *payoffs* (Webb 2007).

- The *players* are the agents playing the game and their behavior is assumed to be rational aiming at making *optimal decisions*. An action a_i is a behavioral choice among a set of alternative available actions A. The set A can be either discrete $A = \{a_1, a_2, a_3, \ldots\}$ or continuous on the interval $[0, 1]$.

- A rule defining which action to take at each decision point is a *strategy*. We define s_i as the particular strategy of player i, and S_i the set of pure possible strategy of player i. A *pure strategy* is a complete plan of actions specifying what player i will choose at each of its information set in a game of perfect information that excludes any randomization. A *mixed strategy* σ assumes randomization over pure strategies that are thus played with certain probabilities (Webb 2007). This means combining pure strategies by weighting them by their probability of occurrence:

$$\sigma = \sum_{s \in S} p(s)s,$$

  where $p(s)$ indicates the probability of occurrence attributed to each pure strategy $s \in S$. A *Best Response* (BR) (Polak 2007) is a strategy that is a best reaction to what each player believes the other player's action will be. The belief is meant to be the factor that rationalizes the player's choice. In more formal terms player i's strategy s_i^* is a BR to the belief p about other players' choices if $Eu_i(s_i^*, p) \geq Eu_i(s_i^{**}, p)$ for all s_i^{**} in S_i, where Eu_i represents the expected payoff (utility) for player i from choosing s_i^* given that she holds the belief p. In other terms s_i^* solves the maximization of $max_{s_i} Eu_i(s_i, p)$.

- A payoff is a function $P : A \rightarrow R$ that assigns to each action a of the set A, a numerical value of the Real set $\mathbb{R}$. If there is uncertainty about payoffs the use of random variables allows to represent payoffs associated to each action a of the set A, given a specific state of nature x of the set X, $P(a|x)$. The payoff then becomes $P(a) = \sum_{x \in X} P(a|x)P(X = x)$, where $P(X = x)$ represents the probability of occurrence of the state of nature x.

An *optimal decision* implies to choose an action a^* of the set A such that the payoff $P(a^*)$ is maximized.

The principle of optimality represents the basic assumption behind the *backward induction* methodology used to solve games. In other words we assume that future decisions will be taken optimally and by working backward the tree we can identify what the current optimal decisions are. The key idea is to look forward to the end of the tree solving for optimal future decisions and work backward through the tree till the solution of the initial node. The methodology can be used directly to solve games of perfect information or adapted to solve games of imperfect information.

In a *game of perfect information*, each information set in the tree refers to only one node (fig 2.3). This means that at every node the history of the game (i.e the previous actions of the players) is known by each player. In theory therefore, a process of backward induction can solve the game. For example, if player 2 chooses strategy d in the upper node and strategy u in the lower node, player 1 will subsequently chose the optimal strategy that will result in a higher payoff ($2 > 1$), in this case strategy D.

When more than one node shares the same *information set*, it becomes impossible for players to distinguish between the nodes; this is known as a *game of imperfect information*. In figure 2.4, for example, player 2 is faced with a situation where two nodes, U and M, are located on the same information set. This means that player 2 is unable to tell whether player 1 chose U or M. Further to this, player 1 is also aware that player 2 is unable to distinguish between U and M. One method to solve the game in these circumstances would be for player 1 to randomize between strategy U and M.

Assuming that each strategy likelihood is $\frac{1}{2}$, the expected payoff of the mixed strategy is the weighted average of each pure strategy included in the mix[3]. Player 1 is going to receive half of the times 4 and half of the times 0 for an expected payoff of 2. This makes player 1 choose this mixed strategy U, M over the D strategy whose best payoff is 1 (Du=1).

[3]In other words player 1 randomizes between U and M, choosing half of the times U and half of the times M.

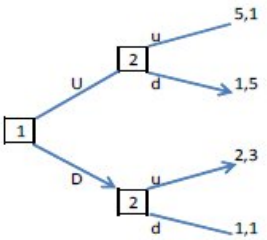

Figure 2.3: Game of perfect information

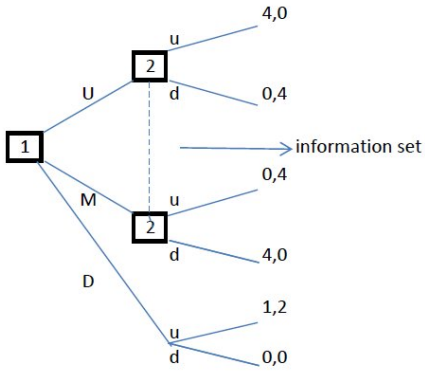

Figure 2.4: Game of imperfect information

Another way to solve more complex games of imperfect information is to use the concept of sub-game perfect equilibrium. The idea involves checking whether the final sub-games represent a Nash Equilibrium (NE) and then working backward to find the NE in all sub-games along the tree. This concept will be further explored later.

Information plays an important role in games. In this respect a distinction is made between *static games* (where players make simultaneous decisions without knowing the other players' choices) and *dynamic or sequential games*. These latter assume that the earlier decisions of others are known by a player when making a given decision. Dynamic or sequential games are represented in the use of decision trees, as per the previous example in fig 2.3 and fig 2.4.

The difference between static and sequential games lies not only in their timing but also in the type of information that is available to the players when making decisions. In static games, players make all their decisions without knowing the decisions or actions of other players in the game. Conversely, in sequential games when player 2 makes his decision, he knows what player 1's move was, and when player 1 makes a decision, he knows that this information will also be available to player 2.

2.3.1 Basic solution rules

One of the most frequently used solutions to solve games is the previously mentioned concept of Nash Equilibrium (NE).

A strategy profile, $(S_1, S_2, \ldots, S_N)$, given N players, is a NE if, for each player i, her choice S_i is a *Best Response* (BR) to the other players' choices S_{-i} (Polak 2007). This concept means that by keeping the strategies of other players' fixed, no player has the incentive to deviate from their own strategy (i.e. there is no improvement in profit by unilaterally changing the strategy). In other words it is the best practice each player can pursue given the others' players strategies.

Before describing a second solution used in dynamic games, called the sub-game perfect equilibrium (SPE), it is important to introduce a definition of a sub-game. A sub-game is a part of a game that looks like a game within the tree; it is essentially a game within a game. To qualify as a sub-game, the following criteria must be met:

- A sub-game must start from a single node
- A sub-game includes all the successors of the node (children, grandchildren, etc.)

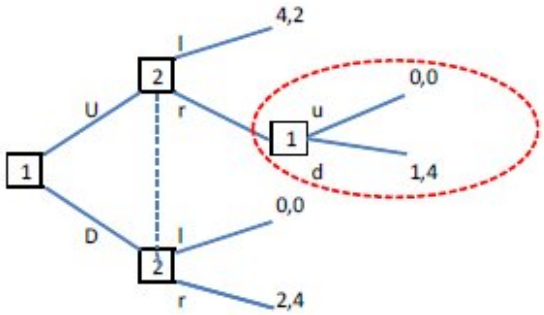

Figure 2.5: Game in extensive form including a sub-game

		player 2	
		l	r
player 1	Uu	4,2	0,0
	Ud	4,2	1,4
	Du	0,0	2,4
	Dd	0,0	2,4

Figure 2.6: Game in normal form including a sub-game

- A sub-game does not break up information sets

The solution to dealing with games that include sub-games is a sub-game perfect equilibrium (SPE). A strategy profile $(S_1, S_2, \ldots, S_N)$ is defined as a SPE if it induces a NE in each sub-game of the game. In summary, a SPE presents the following characteristics:

- SPE is a Nash Equilibrium (NE) and
- SPE induces players to play a NE in every sub-game.

In the following example outlined by (Polak, 2007), the game in figure 2.5 (extensive form) and 2.6 (normal form) is a game of imperfect information with the sub game circled with a dashed line which satisfies the three criteria for sub-games, as listed above.

There are three Nash equilibria (Uu,l) (Du,r) (Dd,r) but the only one that is consistent with backward induction is (Dd,r) - which is also a SPE. In fact, starting from the sub-game player 1 chooses d ($1 > 0$). Moving backwards, player 2 does not know at which node he is, but he does know that if he plays l then he will get either 2 or 0 but if he plays r he will get 4. Therefore player 2 takes the tactical optimal decision, and plays r. Moving a step back, player 1 can choose between U and D. He chooses D with payoff $2 > 1$, and the solution game becomes

(Dd,r). The other two NEs (Uu,l) (Du,r) are not “credible “ as they rely on an “empty threat “ (Fudenberg and Tirole 1985) of player 1 choosing strategy u and player 2 choosing strategy l, which is not a realistic outcome under backward induction.

Generally, a rule of game solution involves firstly identifying the NEs in each sub-game and then rolling backwards to see where the optimal moves are in the tree.

The goal of modeling real options in a game context is to define the equilibrium of strategies. In this context, which differs from a more traditional real option setting, each player's strategy is represented by the simultaneous *Best Response* to the other players' actions (Dias and Teixeira 2010). The equilibrium is found by applying optimization principles using backward induction from the end to the initial nodes along the tree. With this methodology, the resulting strategies are SPE and imply Nash equilibrium in each sub-game.

2.3.2 Option games

Option games integrate game theory with real options and represent a translation of the basic characteristics of game theory within a real option framework (Azevedo and Paxson 2010). In this respect the fundamental element of game theory is the players themselves. In a real option context, ”players” represent the companies facing a real investment option. For example, the option to develop an R&D project for a new molecule. Based on competitive conditions as well as development outcomes, a firm can decide whether to anticipate or defer the project, expand the project in a new indication or stop it. All these outcomes represent the ”strategy” of a company playing a game on the market when faced with uncertain dynamics regarding the demands and pressures that exist through competition. When playing a strategy, each player‘s goal is to reach certain objective results or outcomes which are quantified in numerical terms as payoffs. Payoffs are a means of representing the utility achieved with a certain strategy. Given the uncertainty surrounding the probability of reaching these outcomes, the reference is to expected payoffs. The corresponding terminology for ”payoffs” in real option terms is a company's “value function”. This represents the payoff a firm achieves by playing a specific strategy for any value assumed by the underlying stochastic variables. This dependence on stochastic variables makes the value function rather complex, while the payoff function in standard games are generally represented by simpler, more deterministic values. In the example previously mentioned in section 2.2.1 regarding the two friends deciding on whether to attend the theatre, or the stadium; the payoffs of each player are represented by deterministic

values that represent the utility gained for each player when playing each specific strategy. The difference between deterministic payoffs and value functions has implications in terms of how the equilibrium solutions are defined, as will be shown later.

At this point it is important to highlight that in these situations, uncertainty refers not only to the possibility of obtaining a certain amount of payoff but also to the time taken for its realization, and this will be next explored.

Option games in continuum time

In a real option game setting, each firm needs to not only account for its own optimal strategy, but also for a competitor's optimal option exercise strategy. In game terms, this means that the equilibrium strategies are a company's *Best Response* (Dias and Teixeira 2010).

Firms face uncertainties in an investment opportunity and uncertainty is modeled by fluctuations in the stochastic variable. Firms are assumed to use Markovian strategies leading to Markovian equilibria that depend only on the current state of the stochastic variable. This is because the history at each period can be summarized by the current state of the of the stochastic variable. The current state determines the current payoffs levels (Fudenberg and Tirole 1985).

Option games in continuous form are particularly concerned with the solution of optimal stopping time; that is the identification of the specific strategy that represents an optimal option exercise (Ziegler 2004).

Analogously to pricing perpetual American options, where the firm has no deadline on when to invest, the solution is in continuum and allows for the identification of the threshold x^* which separates the waiting (continuation) area from the stopping area. The continuation area is representative of a waiting strategy interrupted at the threshold x^*, signaling the beginning of the stopping region. The threshold x^* triggers the option exercise thus stopping to wait. The reference is to the first hitting time (or stopping time): the firm invests at the time t^*, the infimum time when the stochastic process X first reaches the value x^* approaching this level from below (Jeanblanc, Yor, Chesney 2009).

The optimal time t^* at which the first player stops is defined in Fudenberg and Tirole (1985) as

$$t^* = \min\{t | a_i^t = \text{stop for at least one } i\}$$

where a_i^t is the $i-th$ player action at time t. If only player i stops at t^* then he gets the leader

payoff and the competitor gets the follower payoff.

Timing issues affect all of a firm's strategies, such as choosing an optimal time to invest so as to to gain the competitive advantage by being the first to patent and preempting others from entering the market. Similarly, the player who is second to the market must decide how much time to dedicate to the development of an improved version of the leader's drug. These are optimal decisions that pharmaceutical firms must make so as to maximize the value of their options.

Option games in discrete time

Option games in discrete time form value R&D opportunities using a binomial tree. In this situation the underlying uncertain variable is analyzed using a two stage game model that considers both upward and downward movements (Smit and Ankum 1993). Basic insights into the investment timing strategy in duopoly are obtained by analyzing SPE and applying backward induction along the tree. Project values, outcomes or payoffs are developed along the tree and are represented in deterministic values (as in standard games).

The level of information available at each decisional node reflects an important element of the game. For example, a situation of perfect information is defined by the knowledge of historical and current details at each node and has different implications than a game of imperfect information. A game of perfect information assumes no uncertainties, which translates in graphical terms in informations sets consisting of single nodes. In this case there is no ambiguity about what has happened. Conversely when information sets include two or more nodes the game is of imperfect information and one of the players does not know what has occurred.

2.4 Review of Literature

In the past years, the theory behind investment decisions has evolved from the NPV rule, to option game approach. This is especially true when dealing with R&D investments where the limitations of the NPV rule are most obvious, primarily because R&D investments are dominated by uncertainty and require a more flexible approach. Neither uncertainty nor flexibility are considered by NPV methodology.

Following the development of option pricing theory in financial markets, the concept of options started to be applied to real assets which generated the real option theory. The main characteristic of real option theory is the value of flexibility. This is especially important

when starting uncertain or risky R&D projects where the investor commits resources in an irreversible way, thus giving up flexibility. For investors, flexibility in option theory is reflected in the different choices made available; providing the option of waiting, abandoning or contracting the project in accordance with economic conditions. Among the first to introduce the value of the option to wait was Mc Donald and Siegel (1986) followed by Majd and Pindyck (1987). Both models are in continuous time and refer to investment decisions made in a monopoly. McDonald and Siegel's model aims at computing an optimal investment time in order to identify the value of the deferral option. This model also provides an opportunity to quantify the value destroyed by investing sub-optimally (too early) according to the NPV rule. The Majd and Pindyck (1987) model emphasizes the importance of the option to wait in uncertain conditions, but focuses on compound options where investment decisions are taken sequentially and built over time. This kind of option is typical of R&D projects where the flow of expenses can be modulated based on new information. Like McDonald and Siegel, the authors show how traditional NPV rules can lead to wrong investment decisions.

Many authors, including Brennan and Schwarz (1985), Pindyck (1986) and Trigeorgies and Mason (1987), explore the concept of irreversible investment under uncertainty, and the opportunity cost (of killing an option) implied by an investment decision. This opportunity represents the option premium, which is disregarded by the traditional NPV approach. A common limitation of these models is that they consider single companies in isolation without accounting for strategic interaction with other firms.

This is a limitation that makes such models inadequate for analyzing real world situations. Here, managerial decisions are influenced by competitors' actions and strategic moves in the market so as to evaluate the possibility of entry by a competitor to the market, and the potential to preempt it.

Only with the application of game theory to real option, the so called option game approach, can the formulation of a strategic attitude become possible. The work of Spencer and Brander (1992) is one of the first examples of duopoly analysis where the trade off between pre-commitments and flexibility is considered. In their study they develop a model to analyze a Stackelberg equilibrium. They conclude that in a case of high uncertainty the leader can give up his first mover advantage and wait until the uncertainty is resolved. Yet despite their reference to flexibility as an option, there is no explicit mention of any real option valuation. Smit and Ankum (1993) were among the first to make the analogy between a real option opportunity and a financial call option. Here the authors highlighted an important difference in

the non-exclusiveness of a real option versus a financial option, and how this can influence an investment strategy. They considered the value of a project and its investment timing strategy under various levels of intensity from competition: from monopoly to perfect competition through oligopoly. The tradeoff is between pre emption leading to a first mover advantage, and the value of waiting. The model is in discrete time and assumes a static game with complete information. The concepts introduced by Smit and Ankum are further developed in the book by Smit and Trigeorgis (2004). Here, the approach is the same, i.e. discrete[4] binomial tree modeling, but the focus of their work is on business practice with several industry and competition examples, as well as exploring the strategy of real options in competitive R&D dynamic. In this latter context, the authors stress how preemption can affect the value of an R&D opportunity and imply value discontinuities. The magnitude of the effect of preemption depends on various factors including: technical uncertainty, the level of incomplete information, the possibility of having learning effects and the firm's attitude to compete versus a more co-operative approach.

Considering option games in continuous time, the Smets' (1991) model is one of the first to consider strategic interactions in a symmetric duopoly market context. By adopting the work of Dutta and Rustichini (1993) on stopping time problems, Smets considers real option optimal exercise under duopoly competition where one's firm revenues flows depends on the other firm's investments decision. Smets' work has provided the foundations from which others have built from (Dixit and Pindyck 1994, Nielsen 2001, Huisman 2001). Dixit and Pindyk's book, (1994) which draws from Smits work in chapter 9, is today considered to be the most widely recognized reference in the real option and game option literature. The authors stress the concept of irreversible investments under uncertainty and the importance of waiting to achieve better information under such conditions. Dixit and Pindyk conclude that the optimal time to invest is when the value of the project exceeds the costs by the amount of the option premium. Nielsen (2001) extended this analysis further. He considered positive and negative externalities and compared the optimal investment strategy of a monopolist with the leader and follower in duopoly. In both cases, the author shows that the leader investment threshold is smaller than the monopolist case.

The impact of externalities and preemption on the investment threshold in duopoly are further analyzed by Mason and Weeds (2001). Here the authors offer a different perspective by considering a setting where the externalities and strategic interactions between firms capture

[4]The exception is represented by chapter 9 of the book that introduces continuous time models

various strategic situations. In particular, for the specific case where preemption and externalities coexist, the time of investment tends to be accelerated. The model assumptions refer to irreversible investment with uncertain returns. In this context solutions are found using a variation of the Dixit and Pyndick (1994) methodology. Instead of the leader being exogenously determined, he is determined endogenously based on the rent equalization principle of Fudenberg and Tirole (1985).

Reiss (1998) introduced an innovative way of looking at competition within the real option games. The author considered the optimal time to adopt and patent a new technology under the assumption that the arrival time of competitors follows a Poisson process. The cash flow dynamics generated by the new technology shows continuous and discontinues changes given by

$$\frac{dCF_t}{CF_{t^-}} = \alpha dt + \sigma dz_t - dq_t,$$

where z is the usual Brownian motion, q_t is a Poisson process, independent of z_t. According to a Poisson process

$$dq_t = \begin{cases} 0 & \text{with probability } (1 - \lambda dt) \\ 1 & \text{with probability } \lambda dt \end{cases}$$

for a time interval dt.

The constant hazard rate λdt represents the intensity of rivalry. When the competitors enter the market, represented by a Poisson event, the project value falls to zero, eliminating monopolistic rent. Reiss' model does not specify a specific kind of competition setting and differs from Mason and Weeds (2001) and Weeds (2002) in its assumption that competition is determined exogenously by the random entry of competitors. This is a limitation common to the earlier real options models (Dias and Teixeira 2010).

Weeds' 2002 model is an important reference for evaluating investments decisions in R&D when faced with two sources of uncertainty: economic and technological. The assumption of "winner takes all" is justified by the existence of a patent system (broadly applied in the R&D context) that guarantees a monopoly rent to the first to make the discovery. In game terms, it represents a zero sum game (Azevedo and Paxon 2010) played in a duopoly market with competition defined endogenously. An application of Weeds' (2002) model to analyze the competition dynamic in the pharmaceutical industry will be considered later in this chapter.

Huisman (2001) presents various game theoretic models, in continuous time, that refer specifically to investments in technology. Huisman's work signaled an important step for-

ward in the incorporation of game theory into real options, especially within the context of new technology adoption. In a real option context, Huisman begins with an exploration of an extension of the Fudenberg and Tirole (1985) and Reinganum (1981) models of a new technology adoption in duopoly. Here, the equilibrium is determined exogenously and endogenously. In the first case one of the firms is given the leader role beforehand. In the second case, more realistically, a firm becomes leader by investing as first. He next considers the case where two or more new technologies become available in a context of uncertain innovation process. He later explores an option game context by extending the basic symmetrical option game of Dixit and Pindyck (1994) and Smets (1991). The innovation of his work lies in the introduction of mixed strategy game equilibrium. In addition to preemption, Huisman further considers a collusion strategy and the possible equilibrium scenarios. A more recent extension of Huisman's (2001) work is presented by Kong and Kwock (2007). The authors argue that the simultaneous investment equilibrium of the Huisman model can never occur under cost asymmetry alone, but rather under both costs and revenue asymmetries.

The Grenadier's book (2000) includes contributions from a variety of influential authors including Kulatilaka and Perotti (1998) who analyze the strategic advantage of growth option under uncertainty and imperfect competition. Their findings were important as they contradicted the traditional view that high volatility is a disincentive for investment growth. They found instead that when the strategic advantage is strong, higher uncertainty encourages investments in growth option because more opportunities are available. The opposite is true when the strategic advantage is weak.

Grenadier (1996) refers to the real estate market and references Williams's model (1993) which considered symmetric and simultaneous equilibrium. In contrast, Grenadier assumes that the equilibrium is endogenously determined as either simultaneous or sequential. The model is in continuous time and allows the dynamics and values of a leader and follower in a duopoly real estate market to be defined. The ultimate goal of Grenadier's works to provide a rationale that explains why building booms occur in times of declining demand, a phenomena known as a recession –induced construction boom.

An important aspect in games is the role of information, particularly where there is incomplete information. Lambrecht and Perraudin's (2003) work adds significant value in this area by assuming that each company has incomplete information on the other firm's cost structure. Each player can infer the costs of the other based on their probability distribution, the density of which is assumed to be uniform. Two firms are involved and the authors consider

the preemption threat in the investment decision of each player. Given the assumption that there will be a first mover advantage and that one player behaves strategically in reaching the optimal, while the other partner is a naïve player, the authors conclude by outlining the optimal investment strategy in presence of competition. Considering the investment boundaries, they find that the threshold determined by the NPV rule is the lowest; that is companies that follow the NPV rule invest sooner. Investment thresholds using real option (without competition) is the highest while the middle investment threshold is the boundary determined by real option with competition.

2.5 Basic real options models

Before introducing the specific model that will be used to analyze real option games in the pharmaceutical industry, the Weeds's model (2002), it is appropriate an introduction of the basic option games models.

The analysis will cover the models in continuum time that constitute the cornerstone of the real option game theory. First of all the model of Mc Donald and Siegel (1986) is analyzed. Despite the model referring to a monopolistic market, it presents principles and methodologies that will be later expanded to cover modeling under competition. Building on the McDonald and Siegel, Dixit and Pindyck (1994) and later Huisman (2001) contribute to develop models that cover the real option approach in a competitive duopoly environment.

Methodologically, the value functions and optimal threshold values are found using either the differential equation method or the expectation method. Similar to American option pricing, the first method is based on the definition of the differential equation that is solved by specifying the boundary conditions (the value matching and smooth pasting conditions). The expectation method considers the expected payoff of the players and the expectation is calculated by referring to the first passage time; the infimum time the stochastic variable reaches the threshold.

2.5.1 The monopoly market

In a monopolistic market McDonald and Siegel(1986) and Dixit and Pindyck's (1994) models, identify the value of the investment opportunity and the optimal investment policy. In this respect, while the value of the investment opportunity is represented by the value of a perpetual call option $F(V, I)$ the optimal investment policy refers to the optimal investment time at

which the project is undertaken. The assumptions underlying the model are as follows:

- the project value V follows a Geometric Brownian Motion (GBM): $\frac{dV_t}{V_t} = \alpha dt + \sigma dZ$, where V represents the state variable, Z the standard Brownian motion, σ the volatility and α the drift of the process.
- markets are complete, perfect and there is no arbitrage
- investment costs I are stochastic with dynamic: $\frac{dI_t}{I_t} = \alpha_1 dt + \sigma_1 dB$.
- the drifts α and α_1, the volatilities σ and σ_1 of the two Brownian motions Z and B are assumed to be constant.
- the discount rate is given by r, the constant risk free rate
- the time horizon is infinite

Based on the assumption of market completeness the contingent claim approach is applied. This means finding an asset X to be perfectly correlated with the project V such that $\frac{dX}{X} = \mu dt + \sigma dZ$. Here μ represents the expected return for the undertaken project and the condition $\mu < r$ (r = riskless interest rate) is required to ensure a finite valuation.

The value of the investment opportunity $F(V, I)$ is determined by considering the standard argument of a portfolio θ that is long the option $F(V)$ and short dF/dV units of the project or equivalently of the asset X perfectly correlated with the project. The differential equation obtained by applying Ito's Lemma is solved subject to the boundaries of smooth pasting and value matching[5] condition . The solution found is the following :

- The investment opportunity is $F(V) = aV^{\beta}$, where the constant $a = (V^* - I)/V^{*\beta}$ and the optimal exercise boundary is $V^* = \frac{\beta}{\beta - 1} I_t$
- The value of β is given by the positive root of the fundamental quadratic equation:

$$\frac{1}{2}\sigma^2\beta(\beta - 1) + (r - \delta)\beta - r = 0$$

that is

$$\beta = \frac{1}{2} - \frac{r - \delta}{\sigma^2} + \sqrt{\left(\frac{r - \delta}{\sigma^2} - \frac{1}{2}\right)^2 + \frac{2r}{\sigma^2}} \Rightarrow \beta > 1$$

[5]The solution is obtained by using the differential method where the differential equations represent the players value functions. In this context the boundaries conditions allow to consider the other player's Best Response (Dias and Teixeira 2010)

The parameter β is function of the risk free rate r, the volatility σ^2 and the convenience yield δ. Particularly $\delta = \mu - \alpha$, that is δ corresponds to the opportunity cost inherent in the decision to defer the project (the greater the δ the greater the cost of holding the investing option). It is represented by the difference between the expected return from the undertaken project μ and the capital appreciation deriving from the project investment α (Gibson Brandon 2007).

The optimal investment policy implies that the company waits to invest when $V < V^*$ while the investment is triggered when $V \geq V^*$.

A closer look to the optimal exercise boundary $V^* = \frac{\beta}{\beta-1} I_t$ allows a comparison with the NPV rule. According to the NPV rule the exercise boundary is given by the value of I (the Investment cost). In a real option context allowing for flexibility, the exercise boundary is $V^* > I$ by the flexibility factor $\frac{\beta}{\beta-1}$. In a monopolistic context the investment is delayed until the critical value of the project V^* is reached, implying an option premium. Dixit and Pindick (1994) found that the threshold value V^* might be two to three times bigger than I, highlighting how misleading the NPV rule can be.

The analysis must be revised in the case of competition, as will be next explored.

2.5.2 The duopoly market and option games

The conclusions reached in monopolistic market conditions require an additional step of analysis in the case of competition. Under these conditions, the value of the option to wait depends on what the other competitors do. Dixit and Pyndick (1994) focused their analysis on the duopoly market where the value of the waiting option still exists but is reduced by the risk of preemption by a competitor.

Building on the work of Smets (1991), Dixit and Pyndick's model assumes that there are two identical (symmetric) risk neutral companies deciding on an investment project that implies an irreversible cost I. One company, the leader, has already invested and enjoys the monopoly payoff of having a first mover advantage. Once the second company, the follower, enters the market, the payoff of the firms becomes a duopoly payoff.

The oligopoly inverse demand relationship given price P in term of quantity Q demanded is $P = YD(Q)$, where P is the unit output price, Q represents the industry output assuming value 0, 1 or 2 depending on the number of active firms, D is the demand function and Y represents the industry uncertain aggregate shock following a GBM process: $dY = \alpha Y dt + \sigma Y dZ$. The volatility σ and the drift rate α are assumed constant with the condition $\mu < r$ (r is

the riskless rate) to ensure a finite valuation[6].

The dynamic game is solved backwards, defining the follower's optimal trigger investment point and value function. The follower's profit flow is represented by $YD(2)$ and the problem to be analyzed is an optimal stopping problem in continuous time. The first step to solving the problem is to define the Bellman equation in the form of a differential equation. The value function is found by solving the differential equation subject to the boundary conditions, amongst which are the value matching conditions and smooth pasting conditions. The following optimal threshold value $Y_2D(2)$ triggering the followers' investment is defined by:

$$Y_2D(2) = \frac{\beta_1}{\beta_1 - 1}\delta I,$$

with β_1 being the same that was found in the monopolist case and δ the convenience yield. Y_2 is the value reached by the stochastic process of the demand shock starting at Y. The analysis of the threshold shows dependency on volatility and a lower β increases the threshold. This is consistent with the intuition, suggesting that in a scenario of big uncertainty waiting for more information on the project is the most appropriate strategy[7].

The follower value function $V_2(Y)$ is given by:

$$\begin{cases} \left(\frac{Y}{Y_2}\right)^{\beta_1}\left[\frac{Y_2D(2)}{\delta} - I\right] & if\ \ Y < Y_2 \\ \frac{YD(2)}{\delta} - I & if\ \ Y \geq Y_2 \end{cases}$$

When the threshold is hit at Y_2 the follower invests and obtains the expected discounted present value of the duopoly cash flow perpetuity, net of the investment outflow I. Essentially, the leader and follower share the cash flow of duopoly in perpetuity and both leader's and follower's profit flow is represented by $YD(2)$. Before the threshold optimal investment point is reached, i.e. when $Y < Y_2$, the follower waits until Y_2 is reached and the value of his strategy is represented by the value of the future investment, appropriately discounted. This implies that the leader will have a larger profit flow $YD(1)$.

Using backward induction, the value of the leader and his optimal threshold is estimated. The assumption is that the follower will maintain a consistent optimal strategy leading to a sub-game perfect equilibrium (SPE).

[6] In other words the integral representing the expected discounted present value of a profit flow could be made indefinitely larger by choosing a larger T, making to wait a better policy and the optimum would not exists.

[7] Cf. equation of β in the previous section 2.5.1 where β decreases when σ^2 increases.

The calculations presented are based on the expectation method. The leader value function is obtained by considering the expected value of the leader profit. This can be broken down into two parts: The expected profit of the monopoly phase and the expected profit of the duopoly phase. The threshold value is calculated by applying first order condition, maximizing the present value of the leader's expected payoff.

The leader value function $V_1(Y)$ is given by :

$$\begin{cases} \frac{1}{\delta} Y D(1) \left[1 - \left(\frac{Y}{Y_2}\right)^{\beta_1 - 1}\right] + \left(\frac{Y}{Y_2}\right)^{\beta_1} \left[\frac{Y_2 D(2)}{\delta} - I\right] & if \;\; Y < Y_2 \\ V_2(Y) = \frac{Y D(2)}{\delta} - I & if \;\; Y \geq Y_2 \end{cases}$$

When $Y \geq Y_2$ both firms have invested and share a duopoly profit in perpetuity. If $Y < Y_2$ then the value function reflects the fact that the monopolist's payoff will be reduced by the entry of the follower at a later time.

2.6 The Weeds's model: introduction

Weeds's model (2002) analyses optimal investments strategies for two companies facing an R&D irreversible investment. If the investment is successful, it will lead to a discovery that will be patented. Here, two kinds of risk are considered: the economic risk reflecting the stochastic evolution of the patent value, and the technical risk. Technical risk refers to the uncertainty that the R&D process will not guarantee that an investment will lead to a successfully patented result. The higher the uncertainty, modeled by a hazard rate representing the probability of success, the lower the chances that the first company to invest will reach a patentable discovery. This aspect is important in understanding a firm's strategy: if the first mover advantage is not guaranteed by a successful result then there may be an incentive to delay the investment decision.

Weeds's work builds on theories that are innovatively considered in parallel: The monopolistic market (introduced in section 2.5.1) with reference to the work of Mc Donald and Siegel (1986) later extended by Dixit and Pindyck (1994) (introduced in section 2.5.2), timing games of entry and exit with reference to Fudenberg and Tirole (1985) and the technological uncertainty of discovery modeled by a Poisson distribution with a constant hazard rate, with reference to Dasgupta and Stiglizt (1980) and Dixit (1988).

Players are assumed to use Markovian strategies leading to Markovian equilibria. The

models analyses two kinds of games that well represent the R&D dynamic: a cooperative case and a non-cooperative case.

The cooperative situation is firstly analyzed and the equilibrium results are used as a benchmark: a cooperating sequential (unconstrained) optimum and a cooperative second best simultaneous (constrained) joint investment where the firms invest at the same point. The latter case may emerge due to difficulties in agreeing on a sequential unconstrained pattern. Within a cooperative situation, therefore, three optimal trigger points are identified: π_1 and π_2 representing the optimal sequential trigger points of a leader and a follower respectively, versus π_C that represents the constrained joint investment trigger. The joint investment trigger (π_C) lies between the optimal sequential leader (π_1) and follower (π_2) trigger points.

The other game setting considered, which is common in an R&D contest, is the non co-operative condition which leads to two kind of equilibria. The first is a preemptive leader and follower pattern and the second is a joint investment equilibrium. The joint investment equilibrium assumes that both firms invest at the same trigger point. There is a continuum of equilibrium points, among which a Pareto equilibrium dominates. This latter coincides with the joint investment equilibrium π_C established in the cooperative game. When comparing the trigger investment point of a non cooperative equilibrium with the optimal cooperative investment pattern, an interesting finding is that investment in a competitive setting is delayed. This seemingly counterintuitive result is explained in term of interactions between the leader and the follower. In being the first to invest, the leader has a higher chance of reaching the patentable innovation. The follower is aware of this condition and reacts faster so as to reduce his option value to delay. Anticipating that this kind of strategic dynamic may lead to a patent race, a potential leader may decide to postpone the decision to invest as to avoid the trigger of a sub optimal patent race .

2.6.1 The Weeds's model: assumptions and game settings

As previously discussed, Weeds's model considers two identical risk neutral companies with an irreversible R&D investment decision. The competitive setting is such that both strive to achieve a patentable innovation and the success of the winner eliminates all profit possibility for the other player. Two kinds of uncertainty are considered: economic and technical.

The economic uncertainty is represented by a patent value π that evolves stochastically according to a geometric Brownian motion: $d\pi_t = \mu\pi_t dt + \sigma\pi_t dW_t$. The parameter μ represents

the drift of the process constraints to the condition $\mu < r$, with r= risk free interest rate, to ensure a positive opportunity cost (δ) to hold the option[8]. The value σ represents the instantaneous standard deviation of the process and dW_t is the normally distributed increment of a Wiener process, $W_t \sim N(0, t)$.

The investment decision to start the R&D investment implies a cost K, but there is no guarantee that this will lead to a successful innovation. The technical uncertainty reflects the fact that discovery arrives randomly according to a Poisson distribution with constant hazard rate $h > 0$[9].

Two assumptions define the setting of the game. The first is that the initial value of the patent π_0 is not enough to have a positive investment return, thus precluding by either players a sudden initial investment decision: $E_0 \int_0^\infty e^{-(r+h)t} h\pi_t dt - K < 0$.

The second assumption states the investment irreversibility; that is if $\theta_i(\tau) = 1$ then $\theta_i(t) = 1 \ \ \forall t \geq \tau$. $\theta(\tau)$ represents the firm's investment status. If the company invested at time τ, it will be active also at a later time t and generally until the game ends (due to a discovery). The decision to invest is the only action the player can take. The game is in fact a stopping time game (Dutta and Rustichini 1993) where the strategic decision is to decide when "to stop" waiting. In this case, the decision is taken at the trigger point π_t reached by the stochastic variable at which the R&D project starts. The firm that makes the discovery will receive the project's net present value (NPV).

2.6.2 The optimal investment timing for a single firm

The stopping time game for the single company refers to the optimal stopping problem:

$$V_u(\pi_t) = \max_T E_t \left(e^{-rT} \int_T^\infty (e^{-(r+h)\tau} h\pi_\tau \tau d\tau) - K \right) \tag{2.1}$$

With T representing the future stopping time at which the R&D project starts.

The problem can be solved (Dixit and Pindyck 1994), as in section 2.5.2, by referring to the methodology used in pricing an American option. The value function of the firm $V_u(\pi)$ reflects the fact that in the continuation region (i.e. where $\pi < \pi_u$) the firm holds an option to invest, where π_u represents the optimal stopping point at which the firm invests. In the

[8] In this respect the condition $r - \mu = \delta$ is applied. Therefore the condition $\mu < r$ must hold to ensure a positive opportunity costs in keeping the option that will not be held indefinitely.

[9] Since arrivals occur randomly, the time to discovery is itself a random variable: a continuous random variable that follows an exponential distribution.

stopping region (i.e. where $\pi \geq \pi_u$) the firm has already invested and is entitled to the value of the patentable discovery. This, in turn, depends on the hazard rate governing the discovery.

$$V_u(\pi) = \begin{cases} B_0 \pi \beta_0 & \text{if } \pi < \pi_u \\ \frac{h\pi}{r+h-\mu} - K & \text{if } \pi \geq \pi_u, \end{cases} \tag{2.2}$$

where $B_0 = \frac{h\pi_u^{1-\beta_0}}{r+h-\mu}$ and $\beta_0 = \frac{1}{2}\left\{1 - \frac{2\mu}{\sigma^2} + \sqrt{(1 - \frac{2\mu^2}{\sigma^2})^2 + \frac{8r}{\sigma^2}}\right\}$ is the positive root of the quadratic equation.

The boundary between the two regions represents the optimal stopping point π_u maximizing eq. (2.1) and is found by applying the value matching and smooth pasting conditions. The value π_u is given by :

$$\pi_u = \frac{\beta_0}{\beta_0 - 1} \frac{(r + h - \mu)}{h} K$$

We notice that there exists a threshold π_u such that the investment decision is optimal if $\pi \geq \pi_u$, conversely waiting is optimal when $\pi < \pi_u$. The investment threshold is influenced by the volatility parameter (through the value of β_0). Intuition suggests that the uncertainty raises the threshold and postpones the decison to invest to obtain new information about the project.

2.6.3 The cooperative benchmark

The cooperative setting assumes that both firms plan their investment cooperatively, i.e. a leader firm invests at π_1 and a follower invests at a later time π_2. The value function of the two combined entities $V_{L+F}(\pi)$ under this investment plan comprises three parts. The first part for $\pi < \pi_1$ where none of the firm has invested, reflects the option value in the continuation region. The second part for $\pi \in [\pi_1, \pi_2)$ reflects a situation where the first company has already invested and is entitled to the NPV of the project net of investment costs: $\frac{h\pi}{r+h-\mu} - K$, while the second still holds the option to invest: $A_1 \pi \beta_1$. The third part, $\pi \geq \pi_2$, reflects a situation where both companies have invested and $(2NPV(\pi) - 2K)$ represents the expected NPV of the patentable project when both firms are active. Intuitively the two firms are entitled to the same value of the project $NPV(\pi) - K$, since they have invested sequentially and they represent two identical distinct entities. Conversely, when the two firms are constrained to invest at the same point they represent an integrated entity with investment costs of $2K$ and arrival rate of $2h$.

$$V_{L+F}(\pi) = \begin{cases} A_0 \pi \beta_0 & \text{for } \pi < \pi_1 \\ \frac{h\pi}{r+h-\mu} + A_1 \pi \beta_1 - K & \text{for } \pi \in [\pi_1, \pi_2) \\ 2NPV(\pi) - 2K & \text{for } \pi \geq \pi_2, \end{cases}$$

The value of parameters is such that $\beta_1 > \beta_0$ with β_1 defined as the solution

$$\beta_1 = \frac{1}{2}\left\{1 - \frac{2\mu}{\sigma^2} + \sqrt{(1 - \frac{2\mu^2}{\sigma^2})^2 + \frac{8(r+h)}{\sigma^2}}\right\}$$

and $NPV(\pi) = \frac{h\pi}{r+2h-\mu}$.

The formulation of the problem also allows the two companies to invest simultaneously i.e. $\pi_1 = \pi_2$. It demonstrates how the sequential investment with $\pi_1 < \pi_2$ is the optimal investment strategy, while the simultaneous investment with $\pi_1 = \pi_2 = \pi_C$ is a second best optimum. The second best optimum takes place when the two firms are constrained to invest at the same point because they cannot agree on an asymmetric pattern.

The second best optimum strategy is defined by the joint investment trigger point π_C[10]:

$$\pi_C = \frac{\beta_0}{\beta_0 - 1} \frac{(r + 2h - \mu)}{h} K$$

and the value function of the single company (or half of the joint company) is given by[11]:

$$V_C(\pi) = \begin{cases} B_C \pi \beta_0 & \text{if } \pi < \pi_C \\ NPV(\pi) - K & \text{if } \pi \geq \pi_C, \end{cases} \tag{2.3}$$

where $B_C = \frac{h\pi_C^{1-\beta_0}}{(r+2h-\mu)\beta_0}$.

It is demonstrated that $\pi_C > \pi_U$. This makes sense to both parties because when the two firms agree on the investment strategy they increase their mutual likelihood of reaching a patentable discovery. Further, this allows them to invest later than the single company, shall this be required by economic conditions. A comparison of the constrained optimum π_C with the unconstrained optima π_1 and π_2 shows that the trigger points are positioned according to the following ranking $\pi_1 < \pi_C < \pi_2$. Intuitively the optimum sequential pattern (π_1, π_2)

[10]The hazard rate is in this case equal to $2h$ and reflects the assumption of having two companies active on the R&D project with independent hazard rates. This will be the case also with the follower investment problem of section 2.6.4

[11]Notice the similarity of results with the single firm case (equation (2.2)), but in this case the integrated entity consists of two research units with costs of $2K$ and arrival rate of $2h$.

reduces the opportunity cost of delay (by investing at π_1) while retaining the option to expand R&D in the future (at π_2). The second best option (π_C) commits all the investments at once, with higher opportunity cost of delay and precluding possibilities of future R&D investments.

2.6.4 The non cooperative equilibrium

The non cooperative game implies two kind of equilibria: an asymmetric leader - follower patter and a joint symmetric equilibrium. The investment strategy and the trigger investment points are determined by each firms' incentive to preempt rivals and, in turn, to avoid being preempted themselves. Such an approach references the work of Fudenberg and Tirole (1985), specifically their definition of a firm's dynamics within a non cooperative equilibrium.

The relative positioning of the value function of the leader $V_L(\pi)$ compared to the value function of a joint investment $V_C(\pi)$ plays a crucial role in determining players' strategies. The relative positioning can lead to the following situations: $V_L(\pi)$ is exceeding or not $V_C(\pi)$ and the two functions intersect in the interval $(0, \pi_F)$ with π_F being the follower trigger point. When $V_L(\pi) > V_C(\pi)$ the game equilibrium is a leader – follower pattern. This refers to figure 2.7, where the concave leader value function lies above the convex cooperative value function. The intuition is that the leader's incentives are too strong to make them pursue a joint investment strategy when they would rather be the first to invest. The follower will then invest at a later point in time π_F, but prior to the optimal joint investment π_C.

In the opposite case in which $V_L(\pi) < V_C(\pi)$ the joint investment strategy is generally preferred since the option value to delay is increased. This refers to figure 2.8, where the cooperative value function lies above the leader value function. Nevertheless, a leader - follower pattern may still arise. This scenario represents a situation where the leader is following a preemptive startegy fearing that its competitor will invest first. Such behaviour leads to lower payoffs for both firms than the coordinated strategy, but it is intuitively justified by a strategy of attacking before the opponent does so.

To identify the equilibrium possibilities, the value functions of the two firms need to be evaluated by solving the game. This type of sequential game can be solved by applying backward induction. This implies planning forward to define the follower's optimal strategy, and then solving backward to derive the leader's optimal investment strategy.

The follower investment problem

The assumption is that the leader has invested. In the same way as is applied for the single company, the value function is derived while simultaneously considering that the Poisson arrival process implies an augmented discount rate to $r + h$. The value function $V_F(\pi)$ is given by:

$$V_F(\pi) = \begin{cases} B_F \pi \beta_1 & \text{if } \pi < \pi_F \\ NPV(\pi) - K & \text{if } \pi \geq \pi_F, \end{cases}$$

Once again, the value function in the continuation region (i.e. $\pi < \pi_F$) represents the value of the option to wait. In the stopping region (i.e. $\pi \geq \pi_F$) it represents the project NPV the firm is entitled to if the investment successfully leads to a discovery. The trigger point at which the follower decides to optimally invest is:

$$\pi_F = \frac{\beta_1}{\beta_1 - 1} \frac{(r + 2h - \mu)}{h} K.$$

With β_1 defined as in section 2.3, it is worth noting that since $\beta_1 > \beta_0$ the follower trigger point is taking place prior to the trigger point in the case of joint investment, i.e. $\pi_F < \pi_C$. What is unclear is the ranking between the follower trigger point and the single company trigger point, i.e. the relation between π_F and π_u. This is due to two conflicting direct effects of the leader activity on the follower. On the one hand, given the fact that the leader has already invested, the follower's expected payoff is reduced. The follower is therefore more inclined to postpone his investment, as compared to the single company case. On the other hand, the leader's reality of being the first to innovate makes the follower accelerate the investment decision and give up the option value of waiting, because the leader is already in movement.

The leader's payoff

To understand the leader's optimal investment strategy, the evolution of his payoff function needs to first be considered. The payoff function, or the expected value of its research project, is defined at the time of investment but is later downward revised when the follower invests. At the point of the investment the leader acts as a single company and his value function is the same calculated as described in section 2.6.2, i.e. $\frac{h\pi}{r+h-\mu} - K$. Once the follower enters the competition a negative effect (given by $B_L \pi^{\beta_1}$) on the leader payoff needs to be considered.

This makes the leader's value function when he invests equal to:

$$V_L(\pi) = \begin{cases} \frac{h\pi}{r+h-\mu} - B_L\pi^{\beta_1} - K & \text{if } \pi < \pi_F \\ NPV(\pi) - K & \text{if } \pi \geq \pi_F, \end{cases}$$

with $B_L = \frac{h^2\pi_F^{1-\beta_1}}{(r+h-\mu)(r+2h-\mu)} > 0$.

The leader investment point is defined as π_L, the trigger point where $V_L(\pi_L) = V_F(\pi_F)$. The rent equalization principle imposes the equality of the two firms' expected payoff at the leader trigger point. This is necessary to maintain the equilibrium: if the payoff was different, either the leader or the follower would have an incentive to deviate. The payoff of the leader is represented by the potential monopolistic position he can obtain by being the first to make the discovery. The payoff of the follower is given by the higher expected value of the discovery since he will be able to enter during more favorable economic conditions. These payoffs must be equal at the leader' s trigger investment point π_L, whose existence is demonstrated by the author.

2.6.5 A graphical analysis and intuition: derivation of the model

As outlined in the previous sections, the Weeds' model presents two possible kinds of equilibria in the non-cooperative setting; a sequential asymmetric leader - follower entry and a simultaneous symmetric entry. The kind of equilibrium depends on the relative position of $V_C(\pi)$ and $V_L(\pi)$. If the condition $V_L(\pi) > V_C(\pi)$ is verified, as it is the case in figure 2.7 a two asymmetric leader – follower equilibria are reached.

The investment dynamics of the leader and follower are defined by the various investment trigger points. These points identify three main investment areas[12]: A first zone defined from 0 to π_L, a second defined from π_L to π_F and the third one from π_F onwards.

In the first investment area the value of the follower is higher than the leader whose patent value is negative; this is due to the investment costs incurred by the leader which are not compensated by an adequate project profitability. In this area the economic conditions are not profitable enough to trigger an investment decision by any of the players. Both firms decide to adopt a wait and see strategy.

In the second area, the value of the leader is higher than the follower. By investing at

[12]This part refers to Chapter 9 of Smit Trigeorgis (2004)

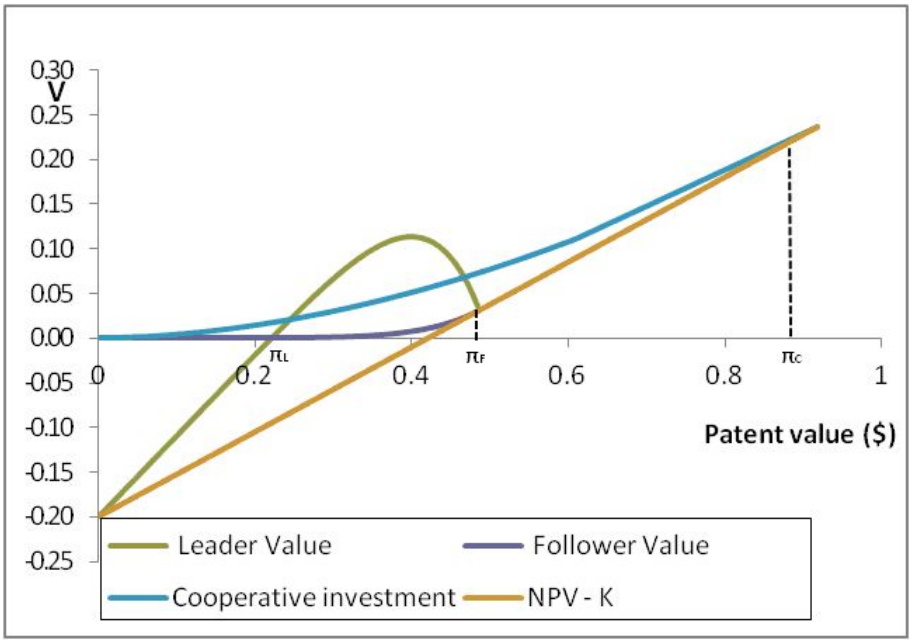

Figure 2.7: Leader and Follower equilibrium

π_L the leader enjoys a temporary monopoly profit up to point π_F when the follower enters the market. In this investment area, the value function of the leader is concave to reflect his monopolistic profit. Conversely, the value function of the follower is a convex function to represent the option value of waiting held by the follower till the trigger investment point π_F. The leader's and follower's value functions intersect at both equilibrium points π_L and π_F. The third investment area, from π_F onwards, reflects a situation where the value function of the leader and follower converge tangentially and both players invest simultaneously. In this area the value of the patent is particularly high and simultaneous investment becomes the optimal policy.

If the condition $V_C(\pi) > V_L(\pi)$ is verified, as it is the case in figure 2.8, the two firms invest jointly at trigger point π_j. There is a set of joint investment equilibria of which the lowest point π_s is defined as: $\pi_s = \inf\{\pi_j \in (0, \pi_C] \mid V_j(\pi; \pi_j) \geq V_L(\pi) \ \ \forall \pi \in (0, \pi_j]\}$, with V_j defined as the value function when both firms invest jointly at an arbitrary point π_j.

Weeds introduces the existence of π_s and how it is unique whenever $V_C(\pi) \geq V_L(\pi) \, \forall \pi \in (0, \pi_C)$. In this case, two types of equilibria exist. Together with the asymmetric leader - follower equilibrium (defined by the trigger points π_L and π_F) there is a joint investment equilibrium (defined by $\pi_j \in [\pi_S, \pi_C]$) where both firms invest jointly. As noted before, π_j is not the only equilibrium trigger point, instead the interval $[\pi_S, \pi_C]$ represents a continuum of equilibrium points. Over the interval no unilateral deviation is profitable; each point is therefore an

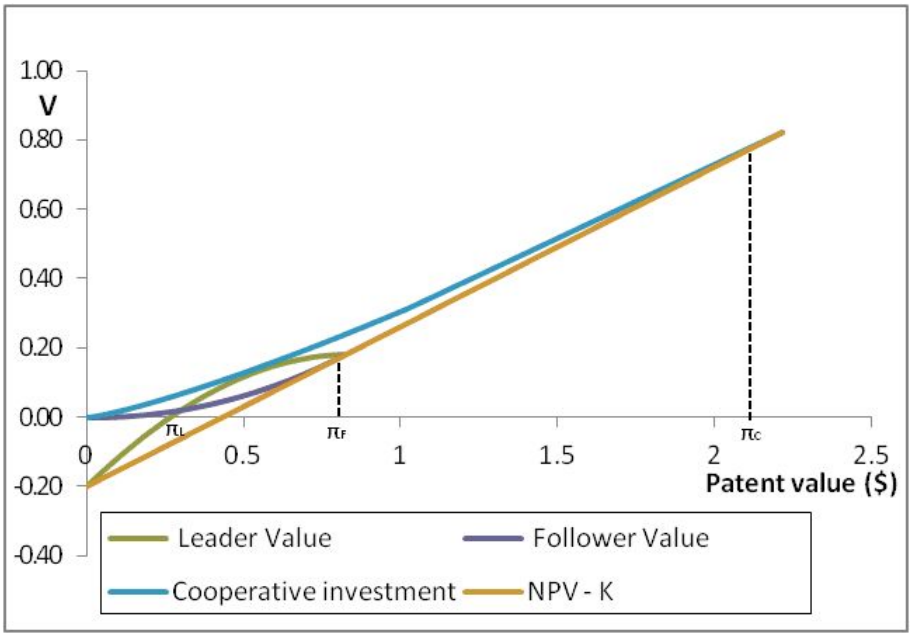

Figure 2.8: Joint Investment equilibrium

equilibrium point. Nevertheless, using the Pareto criterion Weeds demonstrates how multiple equilibrium points can be reduced to one; the trigger equilibrium point represented by π_C. Intuition suggests that cooperation is dominating since negative externalities imposed on the other partner are considered.

A ranking of the trigger points in the various cases as: $\pi_L < \pi_1 < \pi_C < \pi_2$ implies some strategic considerations. Particularly interesting are the following couples of inequalities: $\pi_L < \pi_1$ and $\pi_1 < \pi_C$. The first relationship can be explained as a leader's defensive attack strategy by investing earlier as opposed to adopting a cooperative coordinated strategy. The second relationship shows that in a cooperative setting firms can start the investment earlier, thus reducing the waste of resources.

The analysis so far describes all the cases that can arise in a non-cooperative situation. In practice, however, the application of the model requires the identification of when the various cases take place. To this end, parameters' values need to be considered alongside the existence of a unilateral incentive to deviate from the joint investment. When a player deviates from joint investment he chooses instead to become the leader with a move that the other player is unable to preempt. This can happen only if the leader's payoff is greater than his payoff under joint investment conditions, resulting in unilateral deviation. The immediate implication is that the rent equalization principle is no longer applicable, and smooth pasting and value matching conditions need to be adopted. The application of the two conditions leads to the discovery

of the investment point and the option value $B_D\pi^{\beta_0}$ for the designated leader. An implicit solution for the designated leader's investment point π_D is defined by:

$$(\beta_1 - \beta_0)B_L\pi_D^{\beta_1} + (\beta_0 - 1)\frac{h\pi_D}{r + h - \mu} - \beta_0 K.$$

Once a numerical solution for the trigger point π_D is found, the value of the parameter B_D is given by :

$$B_D = \frac{\pi_D^{-\beta_0}}{\beta_0}\left(\frac{h\pi_D}{r + h - \mu} - \beta_1\beta_L\pi_D^{\beta_1}\right).$$

Comparison between B_D and B_C determines which case holds. This is especially true when an asymmetric leader and follower equilibrium is taking place, $B_D > B_C$. While when $B_C \geq B_D$, the joint investment at π_C is prevalent.

To understand how the model operates, we consider the way numerical analysis can be used to identify the dominant strategy. In this context parameters such as volatility σ, hazard rate h or the drift μ are determinant in defining the shape of the curves representing the value functions (i.e. leader, follower or cooperation strategy) and their relative position. Numerical analysis indicates that a cooperative strategy represents the equilibrium result when, ceteris paribus, volatility σ increases, the hazard rate h decreases or the drift μ increases. Intuitively this can be understood noting that under large uncertainty it is more valuable to adopt a cooperation approach and agree on a common investment strategy. The same holds true when the hazard rate falls, indicating that with a low probably of success putting their efforts together is the most appropriate solution. The consequences for a rising drift (implying a high market potential) can be understood as favoring a cooperative approach. In this case the market perspectives are such to ensure participants a market share that is large enough for profitability. Conversely, a lower market potential is perceived by managers as an indicator of a standalone strategy to earn the value of a limited market share.

Among the parameters mentioned, the volatility is the factor that plays the bigger role. For instance figure 2.7 is referring to a volatility of 10% versus figure 2.8 that is based on a volatility of 50%. We will next proceed with an explanation of how the model works in practice and how the various scenarios can be identified. The first step involves the comparison between the value functions of leader $V_L(\pi)$ and the value function of the cooperative approach $V_C(\pi)$. As highlighted in section 2.6.4 when $V_L(\pi)$ exceeds $V_C(\pi)$, the prevailing strategy is the leader and follower approach, (represented in figure 2.7) since the leader preemptive incen-

tives are too strong to pursue a tactic of cooperation. Conversely when $V_L(\pi)$ is smaller than $V_C(\pi)$ (represented in figure 2.8) a joint investment approach is considered the most appropriate, although in this case a leader and follower strategy could be an equilibrium outcome. Intuitively this is understood as the case of a counterparty that designates herself as a leader and adopts the leadership role as a strategy of attack. This occurs when the leader decides to preempt because it fears that is opponent will do so beforehand. To define the case that is occurring in practice, the comparison between the parameter B_D (indicating a designated leader) and B_C (indicating a joint cooperation strategy) is made.

The implementation of the model requires a discrete approximation of the Brownian motion representing the dynamic of the patent value π. As shown in the appendix each discrete step is defined as a fraction of the follower optimal trigger point π_F. Appendix 6a and 6b refer to calculations necessary to prepare figure 2.7. Notice how at the threshold value π_L corresponding to a time step of 0.24 (reference to appendix 6b) the value functions of the leader and the follower $V_L(\pi)$ and $V_F(\pi)$, are crossing each other and equal[13] to almost zero while the cooperative value function $V_C(\pi)$ is positive and equal to 0.02. Correspondingly the NPV-K value amounts to -0.09 indicating that the project in unprofitable. The threshold π_L represents the trigger point for the leader to invest and the leader value function reaches a maximum (value of about 0.10) in correspondence of π equal to 0.43. At this point the follower convex function starts rising until the follower threshold π_F of 0.53 is reached triggering the follower's investment (reference to appendix 6a).

Appendix 7a and 7b refer to the calculations necessary to prepare figure 2.8. As mentioned, the figure represents a scenario where $V_C(\pi)$ exceeds $V_L(\pi)$ thus implying that the joint cooperative strategy is the most appropriate. Both firms will delay their investment until the threshold π_C is reached at a value of 2.21 when both invest jointly in the project (reference to appendix 7a). Intuitively the investment delay is justified by the option value to delay being more important than the preemptive effect of earlier investment. Nevertheless in this scenario also a leader and follower strategy could be an equilibrium outcome. This would be the case of a designated leader that strategically decides to make the first move so as to preempt the rival. In the specific case a comparison between the parameters B_C (equal to 0.31) and B_D (equal to 0.28) as indicated in appendix 7a, confirms that the joint cooperative strategy is the equilibrium output. The scenario could be reversed by altering parameters: for example by increasing the hazard rate h to 50% and reducing the drift rate μ to 3%. As shown in appendix 7c the scenario

[13]Following the rent equalization principle.

presents a value of B_D (equal to 0.30) and B_C (equal to 0.29), suggesting an asymmetric leader and follower strategy as the equilibrium output. Intuitively this is justified by high probability of success in a context of a reduced market potential both addressing management towards a standalone leader strategy.

The next section covers a numerical analysis with the application of the model to the pharmaceutical industry.

2.7 An application of the model to the Pharmaceutical Industry

The Weeds'model has been chosen in the present study to test the strategic evidence in the life sciences industry. The goal is to verify the model's predictions, as well as to identify the reasons why cooperative behaviors versus non-cooperative behaviors occur.

Various considerations were used to determine the selection of the specific model . First of all, it was important that the model include assumptions underlying technical uncertainty. Indeed, in the pharmaceutical industry the decision to invest has no direct implications in terms of discovery. Discovery depends on the probability of success that the project will lead to a finding. This probability of success is expressed in the model by the hazard rate that governs the chances of a discovery taking place.

Other factors governing model selection relate to strategic considerations. The Weeds' model analyzes when it is appropriate to consider a cooperative approach versus a non co-operative one. This is a crucial aspect in the pharmaceutical industry where the majority of big firms rely on the successes of relatively few blockbuster products. These products are sometimes developed internally, but some are the result of cooperative agreements with third parties such as licensing agreements with academic laboratories or small biotech or joint ventures with other big players. In an industry led by innovation, the cooperative model is a valid business model but not necessarily the preferred one. Such an approach depends on a variety of factors, primarily concerned with the relevant internal competencies of the big player. When a firm can count on skilled researchers with a broad knowledge of the disease area, it maybe less willing to embark on an agreement with an external partner as there may be negligible added value. The possibility of enjoying a larger market share is the discriminating factor. In contrast, when a big player is new to a therapeutic area and cannot count on a skilled and experienced R&D staff, a cooperative solution may be strategically advantageous. The big player can offer financial, development and marketing resources to an innovator partner with fewer

resources, increasing their potential for success, while ensuring a share of the success for the big player.

Finally, as will be further explored in the conclusion, the application of the model offers a better understanding of the firm's behavior and enriches the understanding of the industry's competitive interactions.

2.7.1 Model calibration and empirical results

As previously shown, the model can lead to cooperation versus non-cooperation strategies, depending on parameters values. The parameters of greatest interest in a pharmaceutical context are volatility and hazard rate. Volatility represents the dispersion of the patent value (or project value) over time, and can assume different values depending on the therapeutic area of interest. An estimation of the volatility parameter (as outlined in chapter 1) can be done by considering the sales curve volatility σ^V. Sales are seen as one of the most relevant value driver of the patentable project value, and their volatility can be used as proxy for the model's volatility parameter.

The hazard rate represents the technical probability of success that a compound will move successfully from the preclinical phase through to being launched on the market. As the compound reaches different phases in the development process, the project shows different levels of likelihood that it will successfully reach the market.

For example, when considering two therapeutic areas with different parameters such as the Respiratory area (RESP) and the Cardiovascular (CVM) area, the volatilities are calculated and show different values: a volatility of 34% for the respiratory area and 44% for cardiovascular. The cardiovascular area is an area where the unmet medical need is relatively low and competition is high. In considering the main indication (i.e. hypertension) the possible entry of competitors, including generics, is relatively easy, which is reflected in the market share . This explains the higher volatility than the respiratory area. Here the competition is lower and the market is defined by a small amount of players. For example COPD (Chronic Obstructive Pulmonary Disease), one of the two main indications (the other being Asthma) includes approximately five of the big players[14].

These numerical examples account for the specific parameters of the two therapeutic areas and illustrate the effects of changing the model's parameters, and the identification of a

[14]GlaxoSmithKline, Boehringer Ingelleim , Astra Zeneca , Almirall, Pearl

Model Parameters	
volatility (σ^V)	25% - 50%
discount rate (ρ)	10%
hazard rate (h)	5% - 70%
drift (μ^V)	4%, 5%
convenience yield (δ)	5%, 6%
Investment cost (K)	$0.2

Figure 2.9: Model parameters

preferred strategy.

The assumptions are that the project's patent values follow a Geometric Brownian Motion (GBM) process with constant real drift μ^V and standard deviation σ^V. It can be argued that this assumption does not thoroughly reflect the patent value evolution over time. The dynamics of the sales after patent expiration can follow different patterns not always best represented by a single GBM process. To account for these new considerations an analysis will be performed and the results showed in section 2.9[15].

It is estimated that the RESP area has a drift (growth) rate of about 5% with a volatility of about 34%, versus a drift (growth) rate of 4% and a volatility of 44% of the CVM disease area. The drift represents the growth rate that marketing analysts foresee for the specific therapeutic area over the next 10 years, given the market evolution and competition dynamics.

To obtain a numerical solution, a discrete approximation of the Brownian motion is considered with each discrete step defined as a fraction of the follower optimal trigger points π_F. The assumption of risk neutrality is relaxed and the risk free rate is replaced by the firm's discount rate ρ (the WACC) . The parameters required in the model are stated in figure 2.9.

The firm's discount rate ρ is assumed to be constant at 10%. This determines the convenience yield to be 5% and 6% respectively for RESP and CVM[16]. Investment cost is assumed to be about $0.2.

Numerical analysis is performed by changing the hazard rates (from 5% to 70%, according to the various development phases) for each level of volatility from 25% to 50%. Two sets of

[15]There the assumption of a unique drift of GBM (covering improperly both pre and post patent expiration periods) is replaced with a time dependent drift assuming different values post patent expiry. An estimation of the impact of the patent value is performed under three scenarios.

[16]The condition $\rho = \mu + \delta$ (expressing the equality between returns and growth plus convenience yield), must hold.

analyses are considered, each for the two disease areas. Results of the numerical analysis identify the equilibrium output either as a leader and follower or as a cooperative strategy as reported in figure 2.10 and 2.11.

Starting with the RESP area, an application of a the model with a growth rate (μ^V) of 5% is shown in Figure 2.10. The gray area represents the cooperation strategy and the white area the leader and follower strategy resulting from the model implementation at different levels of volatility and hazard rates. The model results show how the increase of volatility suggests a progressive adoption of a cooperative model. The effect is further supported by a reduced hazard rate, which is typical of the first phase of development. In the extreme case of very high volatility, say 50% , even at phase 3 (where the hazard rate is around 70%) the preferred strategy is still cooperation. In contrast, when the volatility is low a leader - follower pattern is the designated strategy, reinforced by higher levels of hazard rate. Intuition suggests that under large uncertainty, related to study results, a joint cooperative effort between players interacting and exchanging information represents a suitable strategy to manage uncertainty. In the same way when the likelihood of technical success is low, companies tend to integrate their efforts to increase the probability of reaching successful results.

	Phase 1		Phase 2				Phase 3				
volatility (σ^V)	Hazard rate (h)										
	5%	10%	15%	20%	25%	30%	35%	40%	50%	60%	70%
25%	L-F	L-F	L-F	L-F	L-F	L-F	L-F	L-F	L-F	L-F	L-F
27%	C	L-F	L-F	L-F	L-F	L-F	L-F	L-F	L-F	L-F	L-F
30%	C	L-F	L-F	L-F	L-F	L-F	L-F	L-F	L-F	L-F	L-F
32%	C	C	L-F	L-F	L-F	L-F	L-F	L-F	L-F	L-F	L-F
35%	C	C	C	L-F	L-F	L-F	L-F	L-F	L-F	L-F	L-F
37%	C	C	C	C	L-F	L-F	L-F	L-F	L-F	L-F	L-F
40%	C	C	C	C	C	C	C	L-F	L-F	L-F	L-F
42%	C	C	C	C	C	C	C	C	L-F	L-F	L-F
45%	C	C	C	C	C	C	C	C	C	C	L-F
47%	C	C	C	C	C	C	C	C	C	C	C
50%	C	C	C	C	C	C	C	C	C	C	C

Legenda: L-F = Leader and Follower strategy, C= Cooperation strategy

Figure 2.10: Numerical Analysis results (RESP area μ^V =5%)

The model indicates that at a level of volatility of about 25% the leader and follower strategy results are the most appropriate, even at the earlier phase of development when the hazard rate is low. This can be explained by the fact that a project showing low levels of volatility, mainly related to positive results studies, encourages a leader strategy. In fact superior clinical results prompt management to purse the development process as a standalone player. Under those circumstances the awareness of future market potential makes a cooperative approach

	Phase 1		Phase 2				Phase 3				
volatility (σ^V)	Hazard rate (h)										
	5%	10%	15%	20%	25%	30%	35%	40%	50%	60%	70%
25%	L-F	L-F	L-F	L-F	L-F	L-F	L-F	L-F	L-F	L-F	L-F
27%	L-F	L-F	L-F	L-F	L-F	L-F	L-F	L-F	L-F	L-F	L-F
30%	L-F	L-F	L-F	L-F	L-F	L-F	L-F	L-F	L-F	L-F	L-F
32%	L-F	L-F	L-F	L-F	L-F	L-F	L-F	L-F	L-F	L-F	L-F
35%	C	L-F	L-F	L-F	L-F	L-F	L-F	L-F	L-F	L-F	L-F
37%	C	L-F	L-F	L-F	L-F	L-F	L-F	L-F	L-F	L-F	L-F
40%	C	C	L-F	L-F	L-F	L-F	L-F	L-F	L-F	L-F	L-F
42%	C	C	C	L-F	L-F	L-F	L-F	L-F	L-F	L-F	L-F
45%	C	C	C	C	C	L-F	L-F	L-F	L-F	L-F	L-F
47%	C	C	C	C	C	C	L-F	L-F	L-F	L-F	L-F
50%	C	C	C	C	C	C	C	C	C	C	L-F

Legenda: L-F = Leader and Follower strategy, C= Cooperation strategy

Figure 2.11: Numerical Analysis results (CVM area μ^V =4%)

not so interesting from a value added perspective. Conversely the possibility to exploit a larger market share becomes very attractive.

These results can be further interpreted by considering the specific therapeutic areas. The respiratory projects show a definite strategic pattern. Given the low volatility of about 34% the model suggests a cooperative approach only at the very early stages, for example when the project is in phase 1. During the other phases, development should be carried on individually.

Similarly, an application of a the model for the CVM area is considered, but with a growth rate (μ^V) of 4% as shown in (Fig 2.11). These model generic results show a different pattern. All the other parameters (volatility and hazard rate) being equal, the decrease of the growth rate μ^V to 4% makes the model favor the leader and follower strategy. The white area representing the leader and follower strategy is wider than in the previous case (figure 2.11). A lower growth rate implies a lower market potential. In business terms this is perceived by management as a sign to pursue a standalone leader strategy with the aim to appropriate the whole value of a declining market share.

Only at a level of volatility higher than 40%, with low levels of hazard rate like in Phase 1 and Phase 2 of development, is the cooperative approach advised. Intuition suggests that uncertainty on the development results, coupled with high level of volatility related to study results, encourages a cooperative strategy. According to the model, the CVM projects' whose volatility is around 44% should be carried ahead in a cooperative form during phase 1 and phase 2 of development. From phase 3 onwards, however, a leader and follower strategy would be more appropriate.

2.8 Summary

Comparing the applications of the model to the two disease areas (Respiratory and Cardiovascular), the variation in the results, as determined by a reduction in the growth rate μ^V, can be interpreted in terms of market dynamics.

A decrease in the future growth rate μ^V, restricts future market opportunities and the patent value, making the cooperative approach less interesting in business terms. This can be explained by the following rationale: given a reduction in market opportunities, the strategy aims to reinforce individual development and marketing resources to appropriate a limited patent value given a declining market share.

The indications of the model could be reversed in real business practice due to some competitive factors and this will be analyzed in chapter 3. As discussed, a firm's main driver behind a strategic decision that favors a cooperative approach is determined by the level of specific knowledge surrounding a given disease area. A high level of competence and knowledge in the disease area of CVM, for example, coupled with high competition, could make the cooperative approach, contrary to the model's suggestion, less favorable. The reverse is true for the respiratory disease area. Here, the products are generally more complex because they are administered with a respiratory device. Together with lower levels of competition this could make the licensing and joint venture strategy particularly interesting.

2.9 A model adaptation to the Pharmaceutical Industry

As previously mentioned, the assumption of patent value that evolves exogenously following a Geometric Brownian Motion (GBM) suffers limitations when representing the cash flows dynamics of a pharmaceutical product due to the drug patent expiration. After patent expiration, the firm loses market exclusivity as generics start entering into the market. This can be supported by analyzing the volume erosion curve after patent expiration of a hypertensive product, as shown in Figure 2.12. Here, the Loss of Exclusivity (LOE) curves of Losartan, the first oral angiotensin II antagonist indicated in the treatment of Hypertension, vary greatly from country to country. For example, sales volumes in the UK, USA and Germany erode rapidly when compared to those of China, Belgium and Italy. Figure 2.12 therefore shows how rather different sales dynamics are determined by the entry of generics.

In terms of GBM, the patent value evolution can be represented by more than one stage.

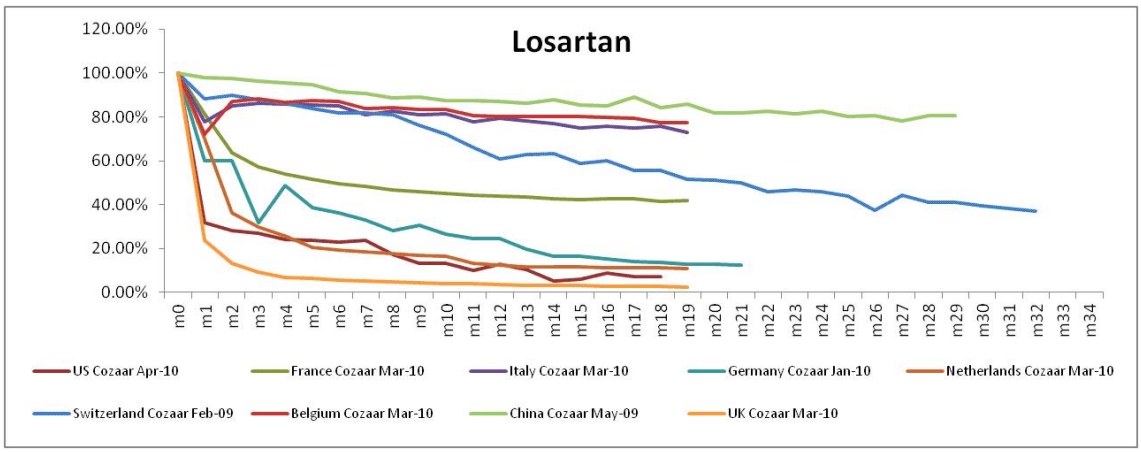

Figure 2.12: Losartan LoE.

In the first stage, there is a positive drift covering the period from the launch to patent expiration. Here, the positive drift represents the constant growth of a product enjoying market share protection through patent exclusivity. The second stage represents the point of patent expiration, when generics enter the market. As highlighted in Figure 2.12, this can result in different dynamics. Either the cash flow (driven by sales) declines dramatically (as in the case of the US market) or it remains (as per the China market). In the first case, the dynamic could be represented with negative drift while in the second case a drift equal to zero would be appropriate. The next chapter further explores the analysis described above.

2.9.1 Value of the firm in presence of two regimes, one stochastic process and two states for the drift

Section 2.7 covered an application of the Weeds's model in the pharmaceutical business. The interesting aspect of the model is that it allows the derivation of optimal strategies in a market with competition; however it presents a significant limitation related to the dynamic of cash flows. By stating that cash flows evolve exogenously growing at an exponential rate over time and after patent expiration, the company value is overstated. As mentioned, such unrealistic assumption doesn't adequately reflect cash flows trends over the life cycle of a drug. The assumption of a unique drift is therefore replaced with a time dependent drift that assumes different values before and after patent expiry. The new setting is outside the Weeds's model and assumes that the firm invests at time $t = 0$. Thus, there is no future optimal time to start the investment. This simplifies the calculation of the firm value and allows us to focus on the impact of the modeling choice of future cash flows (subject to discovery) on the firm value.

The R&D cost is fixed and occurs at time $t = 0$.

The value of cash flows π_s evolves exogenously and stochastically according to a GBM process: $\frac{d\pi_t}{\pi_t} = \mu_t dt + \sigma dW_t$.

As in Weeds's model: the firm receives cash flows π_s only after discovery. Importantly, the stochastic process of cash flows is completely exogenous and disconnected from the time of discovery. One way to think about it is the following: the process of cash flows is latent but materializes (and is received and accumulated by the firm) only after the discovery. Economically, it might sound odd, but this modeling approach simplifies the calculations.

Firm value at time $t = 0$, provided that no discovery has occurred until time 0

$$V_0 = E_0 \int_0^\infty e^{-rs} \pi_s \, \mathbb{I}(s > Z) \, ds - K \tag{2.4}$$

$$= \int_0^\infty e^{-rs} E_0[\pi_s \, \mathbb{I}(s > Z)] \, ds - K \tag{2.5}$$

where E_0 is time-0 conditional expected value, r is the appropriate discount rate of future cash flows π_s, Z is the random time of the discovery, $\mathbb{I}(s > Z) = 1$ when $s > Z$ and zero otherwise, K is the time-0 value of the R&D costs.

The random time $Z \sim Po(h)$ is exponentially distributed with parameter h and independent of the cash flow process π_s.

The second equation above shows that the key quantity to calculate to compute the firm value is

$$E_0[\pi_s \, \mathbb{I}(s > Z)]. \tag{2.6}$$

We now compute this quantity. For simplicity, we assume that the cash flow π_s follows a GBM with constant drift, i.e., $d\pi_s/\pi_s = \mu \, ds + \sigma \, dW_s$. Thus, for $0 < s$, $E_0[\pi_s \, \mathbb{I}(s > Z)]$ is equal to

$$E_0[\pi_s \, \mathbb{I}(s > Z) | s > Z] \, Pr(s > Z) + E_0[\pi_s \, \mathbb{I}(s > Z) | s < Z] \, Pr(s < Z) \tag{2.7}$$

$$= E_0[\pi_s \, \mathbb{I}(s > Z) | s > Z] \, Pr(s > Z) + 0 \tag{2.8}$$

$$= E_0[\pi_s \times 1 | s > Z] \, Pr(s > Z) \tag{2.9}$$

$$= \pi_0 e^{\mu s}(1 - e^{-hs}) \tag{2.10}$$

as $Pr(s > Z) = 1 - e^{-hs}$. Using the last expression for $E_0[\pi_s \mathbb{I}(s > Z)]$, the firm value is

$$\begin{aligned} V_0 &= E_0 \int_0^\infty e^{-rs} \pi_s \mathbb{I}(s > Z)\, ds - K && (2.11)\\ &= \int_0^\infty e^{-rs} E_0[\pi_s \mathbb{I}(s > Z)]\, ds - K && (2.12)\\ &= \int_0^\infty e^{-rs} \pi_0 e^{\mu s}(1 - e^{-hs})\, ds - K && (2.13)\\ &= \pi_0 \int_0^\infty e^{-rs} e^{\mu s}(1 - e^{-hs})\, ds - K && (2.14) \end{aligned}$$

An alternative way of calculating $E_0[\pi_s \mathbb{I}(s > Z)]$ is the following. The idea is to realize that the discovery Z (which is a random variable) can occur any time between time 0 and time s. For each one of these times (or events) π_s is non-zero because time $s > Z$. There is no need to consider events in which the time of discovery $Z > s$ because in such events the cash flow is zero. More precisely, the idea is to consider the cash flow, condition on the time of discovery $Z = z$ and then multiply by the probability (density) of this event.

$$\begin{aligned} E_0[\pi_s \mathbb{I}(s > Z)] &= \int_0^s E_0[\pi_s \mathbb{I}(s > Z) | Z = z] Pr(Z \in dz) && (2.15)\\ &= \int_0^s E_0[\pi_s \mathbb{I}(s > Z) | Z = z] h e^{-hz}\, dz && (2.16)\\ &= \int_0^s E_0[\pi_s \times 1 | Z = z] h e^{-hz}\, dz && (2.17)\\ &= \int_0^s \pi_0 e^{\mu s}\, h e^{-hz}\, dz = \pi_0 e^{\mu s} \int_0^s h e^{-hz}\, dz = \pi_0 e^{\mu s}\,(1 - e^{-hs}) && (2.18) \end{aligned}$$

which is the same result as above, as expected.

Using the first expression of $E_0[\pi_s \mathbb{I}(s > Z)]$ with $Pr(Z \in dz)$, the firm value reads

$$\begin{aligned} V_0 &= E_0 \int_0^\infty e^{-rs} \pi_s \mathbb{I}(s > Z)\, ds - K && (2.19)\\ &= \int_0^\infty e^{-rs} E_0[\pi_s \mathbb{I}(s > Z)]\, ds - K && (2.20)\\ &= \int_0^\infty e^{-rs} \int_0^s E_0[\pi_s \mathbb{I}(s > Z) | Z = z] Pr(Z \in dz)\, ds - K && (2.21) \end{aligned}$$

The random time Z is exponentially distributed with parameter h and disconnected from the cash flow process π_s. The intensity of discovery h is constant over time.

As in Weeds's model, the cash flows π_s are stochastic, exogenous and received only after the discovery occurs, i.e., $s > Z$. The disconnection of Z and π_s implies that $E_0[\pi_s \mathbb{1}(s > Z)] =$

$E_0[\pi_s]E_0[\mathbb{1}(s > Z)]$. Thus,

$$V_0 = \int_0^\infty e^{-rs} E_0[\pi_s]\, E_0[\mathbb{1}(s > Z)]\, ds - K$$

where $E_0[\mathbb{1}(s > Z)] = E[\mathbb{1}(s > Z)] = Pr(s > Z) = 1 - e^{-hs}$ represents the probability of discovery.[17]

Considering the GBM $\frac{d\pi_t}{\pi_t} = \mu_t dt + \sigma dW_t$ and $E_0(\pi_s) = \pi_0 e^{\mu s}$ when μ is constant and given that the value 0 represents the initial time and $\bar{t}$ the time of patent expiry, the cash flows dynamic becomes:

$$\frac{d\pi_t}{\pi_t} = [\mu_+ \mathbb{1}(s \leq \bar{t}) + \mu_- \mathbb{1}(s > \bar{t})]dt + \sigma dW_t$$

Considering $\frac{d\pi_t}{\pi_t} = \mu_t dt + \sigma dW_t$, when μ_t is a deterministic function[18] of time and applying Ito's lemma, the expectation is calculated as $E_0(\pi_s) = \pi_0 e^{\int_0^s \mu_u du}$.

Therefore the expected value of the patent cash flows at the instant s is given by the discontinued function:

$$E_0(\pi_s) = \begin{cases} \pi_0 e^{\int_0^s \mu_+ du} = \pi_0 e^{s\mu_+} & \text{when} \quad 0 \leq s \leq \bar{t} \\ \pi_0 e^{\int_0^{\bar{t}} \mu_+ du + \int_{\bar{t}}^s \mu_- du} = \pi_0 e^{\bar{t}\mu_+ + (s-\bar{t})\mu_-} & \text{when} \quad \bar{t} \leq s \end{cases} \tag{2.22}$$

where μ_+ and μ_- are suitable drifts chosen to reflect the dynamic of cash flows affected by patent status. It should be noted that equation (2.22) is flexible enough to accommodate for all the various scenarios (positive drift of cash flows before patent expiry, zero or negative drift of cash flows after patent expiry). Notice that the assumption of exogenous cash flows following a GBM with two drifts is not ideal, but it is a better representation of reality than a GBM with only one drift (as in the Weeds' model). The assumption of exogenous cash flows will be later relaxed.

2.9.2 Comparative statics

The results summarized in equation (2.22) in the previous section represent the expected value of a patent's cash flow under the following assumption: the cash flow dynamics after patent expiration are represented by different GBM stages. The first scenario involves a sharp declining market share after patent expiration, and the second represents a constant dynamic after

[17] For a general valuation time t_0 this would be $1 - e^{-h(s-t_0)}$.

[18] This represents a general case. In the specific case of $\mu_u = \mu$, that is μ is constant, the expression becomes $\pi_t e^{\int_t^s \mu du} = \pi_t e^{\mu(s-t)}$

patent expiration. In the context of the Losartan example shown previously in Figure 2.12, this is exampled by comparing the USA sales dynamics and the China sales dynamics after patent expiration. It is next important to explore some comparative statics so as to estimate a change in a company's value under the following three scenarios:

1. Scenario 1: Here the assumption is that the patent's cash flows follow a GBM with positive drift

2. Scenario 2: Where two GBM are identified as a primary period with positive drift and a secondary period with negative drift following patent expiration. This would likely reflect the case of the USA market presented in Figure 2.12.

3. Scenario 3: Where two GBM are identified by a primary period with positive drift and a secondary period with zero drift after patent expiration. As was the case of the China market presented in Figure 2.12.

The parameters to calibrate over time for the three scenarios identified above are the following:

$$(h, \pi_0, \mu_+, \mu_-, K, \bar{t}).$$

Given the expected value of the patent cash flows as defined above by equation (2.22) the general formula representing the value of the company can be derived as follow:

$$V_0 = \int_0^{\bar{t}} e^{-rs}\pi_0 e^{s\mu_+}(1 - e^{-hs})ds + \int_{\bar{t}}^{\infty} e^{-rs}\pi_0 e^{\bar{t}\mu_+ + (s-\bar{t})\mu_-}(1 - e^{-hs})ds - K, \tag{2.23}$$

where the expression $1-e^{-hs}$ represents the probability of discovery, K the costs of investment and e^{-rs} the discount factor.

The analysis proceeds by estimating the firm's value under the three scenarios.

Scenario 1

Here, the patent's cash flows evolve exogenously and stochastically according to a single GBM process, as assumed in the Weeds' model. The GBM is unique with a constant positive drift covering both time frames: the period from launch up to patent expiry and the period after patent expiry. Based on the following parameters values:

$$h = 50\%, K = 200, \pi_0 = 40, \mu_+ = 4\%, \mu_- = 4\%, \bar{t} = 10, r = 10\%.$$

The value of V_t is estimated based on eq. (2.23) as being equal to 575.

Scenario 2

In this instance, the patent's cash flows evolve exogenously and stochastically according to two GBM processes. A first process, with a positive drift representing the increasing cash flows trend from launch to patent expiry; a second process with a declining drift reflecting the decrease in cash flows after patent expiry. Based on the following parameters values:

$$h = 50\%, K = 200, \pi_0 = 40, \mu_+ = 4\%, \mu_- = -4\%, \bar{t} = 10, r = 10\%.$$

The parameters used are the same as in Scenario 1 with the exception of the drift that assume values $+4\%$ and -4% over the periods before and after patent expiry respectively.

The value of V_t is estimated based on eq. (2.23) as being equal to 135.

Scenario 3

Here, the patent's cash flows evolve exogenously and stochastically according to two GBM processes. A first process with a positive growing drift represents the increasing cash flows from launch to patent expiry; a second process with constant drift reflects the constant cash flows trend after patent expiry. Based on the following parameters values:

$$h = 50\%, K = 200, \pi_0 = 40, \mu_+ = 4\%, \mu_- = 0\%, \bar{t} = 10, r = 10\%.$$

The parameters used are the same as in the previous scenarios with the exception of the drift that assume values $+4\%$ and 0% over the periods before and after patent expiration respectively..

The value of V_t is estimated based on eq. (2.23) as being equal to 249.

The analysis is repeated under the assumption that parameter h, representing the intensity of discovery rate, assumes values h=20% and h=80%. A value of h=20% represents a low intensity of discovery, while h=80% represents a rather high probability of reaching a discovery. Figure 2.13 summarizes the comparative statics analysis:

Numerical results show the importance of a change in the drift on the firm value. All scenarios show that going from a positive drift of 4% to a negative drift of -4% firm value is heavily reduced. This reduction is particularly important at low levels of h. When h=20% firm value moves from 487 to 58 showing a decline of about 88%. The reduction is slightly lower

h μ	4%	0%	-4%
20%	487	168	58
50%	575	249	135
80%	600	274	159

Figure 2.13: Comparative statics

74%, (with firm value going from 600 to 159) when h=80%. It appears that low intensity discovery rates make the impact of a change in the drift μ somewhat more important. Intuitively this can be explained by the fact that low discovery rates put the firm cash flows at risk since the likelihood of a successful discovery is low. In a context of a firm with risky cash flows, a reduction in the drift has a compounding negative effects on the firm value.

2.9.3 Model Extension (General case)

One limitation of the model above is that the cash flows π_s are exogenous and disconnected from the time of discovery Z. In practice, this assumption may be violated, especially when the cash flows have time-dependent drifts, as μ_+ and μ_-.

A more realistic modeling approach is to assume that the inverse-V shape of drifts starts at the time of discovery. The inverse-V shape is determined by a positive drift followed by a negative or zero drift as stated in the previous paragraph. Notice that this situation is approximately captured in the model above when the intensity of the discovery rate is sufficiently high.

From a mathematical perspective, the new model setting is challenging because π_s and Z are no longer independent. The firm value at $t = 0$ is still

$$V_0 = E_0 \int_0^\infty e^{-rs} \pi_s \, \mathbb{1}(s \geq Z) \, ds - K$$

$$= \int_0^\infty e^{-rs} E_0[\pi_s \, \mathbb{1}(s \geq Z)] \, ds - K$$

However, the conditional expectation is no longer easily calculated. Using the law of iterated

expectations, the firm value takes the form

$$V_0 = \int_0^\infty e^{-rs} \int_0^s E_0[\pi_s \, \mathbb{1}(s \geq Z)|Z = z]P(Z \in dz)\, ds - K$$

$$= \int_0^\infty e^{-rs} \int_0^s E_0[\pi_s \, \mathbb{1}(s \geq Z)|Z = z]he^{-hz}\, dz\, ds - K$$

$$= \int_0^\infty e^{-rs} \int_0^s E_0[\pi_s|Z = z]he^{-hz}\, dz\, ds - K \tag{2.24}$$

The inner conditional expectation (i.e., conditional on the event that the discovery occurs at time z) can now be calculated

$$E_0[\pi_s|Z = z] = \pi_z e^{\int_z^s \mu_u \, du}$$

when $s > z$ and assuming that the starting level of future cash flows π_z is known at time $t = 0$ and the drift μ_u is time-varying but deterministic function of time[19]. If this is not the case, then the right hand side will be $E_0[\pi_z e^{\int_z^s \mu_u \, du}]$, where the expectation is over the relevant random variables (including the future initial level of cash flows and stochastic drift).

In general, the firm value in equation (2.24) is not available in closed-form. Under specific but relevant cases it is available in closed-form. To get an understanding of how the probability of discovery h can impact the firm value, consider the following example. Suppose $\pi_z = \bar{\pi}$ and $\mu_u = \bar{\mu}$, then

$$V_0 = \int_0^\infty e^{-rs} \int_0^s \bar{\pi} e^{(s-z)\bar{\mu}} he^{-hz}\, dz\, ds - K = \frac{h\bar{\pi}}{(r - \bar{\mu})(h + \bar{\mu})} - K$$

As usual, $r > \bar{\mu}$ to ensure the convergence of the integrals above. As expected, the analytical expression shows that the larger the initial future cash flow $\bar{\pi}$, the larger the value of the firm. Notice that increasing the constat drift $\bar{\mu}$ of future cash flows has a somewhat unexpected impact on the firm value (as it appeared in the denominator). The reason is that increasing $\bar{\mu}$ implies (implicitly) that the discount rate r should increase as well, to obtain a finite firm value. Also, when the probability of the discovery becomes very large (or more precisely when the hazard rate of the discovery becomes very large), the firm value approach the asymptotic value of $\frac{\bar{\pi}}{(r-\bar{\mu})(1+\bar{\mu})} - K$. In this case, the firm value can be increased only by improving future cash flows or reducing R&D costs. Intuitively this is explained by noting that the firm can create

[19]Notice that μ_u can assum values μ_+ and μ_- since this is a general case.

more value either by managing R&D costs more efficiently, or by enhancing value creating activities leading to higher cash flows.

Suppose for example r=10%, $\bar{\pi}$ =1, $\bar{\mu}$=4%, K=0.2. When the hazard rate of discovery h is equal to 0%, the firm's value is equal to -0.2, that is in the absence of discovery the business assumes a negative value equal to the R&D investments costs. Conversely, when the hazard rate of discovery h is equal to 100% and the company successfully reaches a discovery, the firm's value tends asymptotically to 16. The analysis is repeated for higher values of $\bar{\mu}$=6% and 8%. Figure 2.14 reports the company's valuation for the range of values assumed by the parameter h.

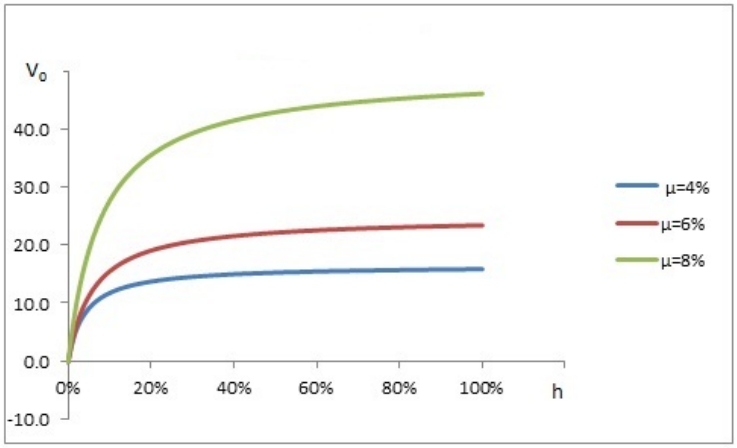

Figure 2.14: Company's value (function of h)

A further analysis considers how the value of the company changes as a function of the growth rate $\bar{\mu}$. Correspondingly specific values of the hazard rate of discovery h are selected for early development stages (h= 5% and 10%) and more advanced development stages (h=50% and h=90%). Notice that when $\bar{\mu}$ is equal to 0% the firm's value is independent from the value of h and is worth 10. Intuition suggests that the lack of growth possibilities inhibits the possibility of successful discoveries, whereas increasing levels of growth trigger higher firm's values especially in correspondence of more likely rates of success h. Figure 2.15 summarizes the positive impact of growth rate $\bar{\mu}$ and hazard rate of discovery h on the firm's value.

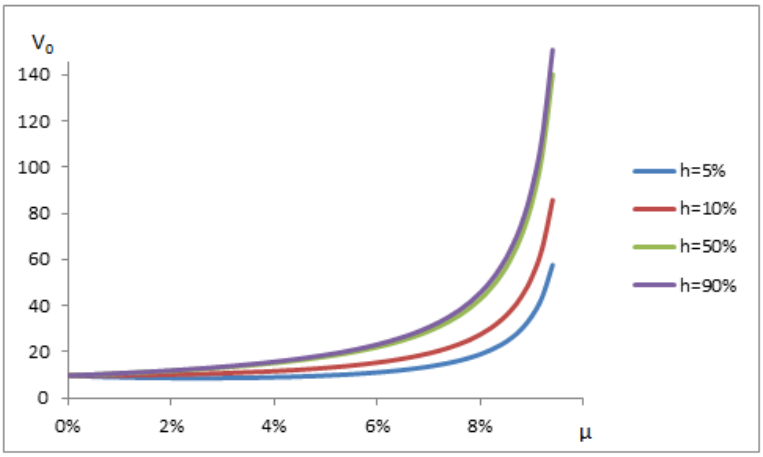

Figure 2.15: Company's value (function of $\bar{\mu}$)

2.9.4 Model extension (Specific case)

Suppose now the drift of the cash flow depends on the time of discovery (because patent expiries x years after discovery). In this case the cash flow process is more complicated $d\pi_s/\pi_s = \mu(Z)\,ds + \sigma\,dW_s$.

The firm value at time $t = 0$ is still

$$V_0 = E_0 \int_0^\infty e^{-rs} \pi_s \mathbb{I}(s > Z)\,ds - K \tag{2.25}$$

$$= \int_0^\infty e^{-rs} E_0[\pi_s \mathbb{I}(s > Z)]\,ds - K \tag{2.26}$$

and it is still the case that

$$E_0[\pi_s \mathbb{I}(s > Z)] = \int_0^s E_0[\pi_s \mathbb{I}(s > Z)|Z = z] Pr(Z \in dz) \tag{2.27}$$

$$= \int_0^s E_0[\pi_s \mathbb{I}(s > Z)|Z = z] h e^{-hz}\,dz \tag{2.28}$$

$$= \int_0^s E_0[\pi_s \times 1|Z = z] h e^{-hz}\,dz \tag{2.29}$$

However, what is different is the conditional expectation: $E_0[\pi_s|Z = z]$. Assume that π_z is known at time 0 and that $\mu(Z)$ is a deterministic function of time,

$$E_0[\pi_s|Z = z] = \pi_z e^{\int_z^s \mu_u\,du} \tag{2.30}$$

For example, if the time line is the following: discovery at time z, patent expiry after x years. When s is after the patent expiry

$$E_0[\pi_s|Z=z] = \pi_z e^{\int_z^s \mu_u\, du} = \pi_z e^{((z+x)-z)\mu_+ + (s-(z+x))\mu_-} \tag{2.31}$$

In general, when z is the time of discovery and patent expires after x years

$$E_0[\pi_s|Z=z] = \begin{cases} \pi_z e^{(s-z)\mu_+} & \text{when } z < s < z+x \\ \pi_z e^{x\mu_+ + (s-(z+x))\mu_-} & \text{when } z+x < s \end{cases} \tag{2.32}$$

We now compute the firm value when the cash flow drift is given by (2.32). At time 0 the expected starting value of the cash flow at time $Z = z$ (i.e., when the discovery occurs) is $E_0[\pi_z|Z=z] = \overline{\pi}$, which does not depend on z (to simplify calculations).

Recall that $\mu_- < 0 < r < \mu_+$. For the integrals above to converge, it must be that $\mu_- < r$, but this is not a restriction.

Firm value:

$$\begin{aligned}
V_0 &= E_0 \int_0^\infty e^{-rs}\pi_s\, \mathbb{I}(s > Z)\, ds - K && (2.33)\\
&= \int_0^\infty e^{-rs} E_0[\pi_s\, \mathbb{I}(s > Z)]\, ds - K && (2.34)\\
&= \int_0^\infty e^{-rs} \int_0^s E_0[\pi_s\, \mathbb{I}(s > Z)|Z=z] Pr(Z \in dz)\, ds - K && (2.35)\\
&= \int_0^\infty e^{-rs} \int_0^s E_0[\pi_s\, \mathbb{I}(s > Z)|Z=z] h e^{-hz}\, dz\, ds - K && (2.36)\\
&= \int_0^\infty \int_0^s e^{-rs} E_0[\pi_s|Z=z] h e^{-hz}\, dz\, ds - K && (2.37)\\
&= \int_0^\infty \int_z^\infty e^{-rs} E_0[\pi_s|Z=z] h e^{-hz}\, ds\, dz - K && (2.38)\\
&= \int_0^\infty \int_z^\infty e^{-rs} E_0[\pi_s|Z=z]\, ds\, h e^{-hz}\, dz - K && (2.39)\\
&= \int_0^\infty \left(\int_z^{z+x} e^{-rs} E_0[\pi_s|Z=z]\, ds + \int_{z+x}^\infty e^{-rs} E_0[\pi_s|Z=z]\, ds \right) h e^{-hz}\, dz - K && (2.40)\\
&= \int_0^\infty \left(\int_z^{z+x} e^{-rs} \overline{\pi} e^{(s-z)\mu_+}\, ds + \int_{z+x}^\infty e^{-rs} \overline{\pi} e^{x\mu_+ + (s-z-x)\mu_-}\, ds \right) h e^{-hz}\, dz - K && (2.41)\\
&= \int_0^\infty \left(\frac{e^{-r(x+z)}(e^{rx} - e^{x\mu_+})\overline{\pi}}{r-\mu_+} + \frac{e^{-r(x+z)+x\mu_+}\overline{\pi}}{r-\mu_-} \right) h e^{-hz}\, dz - K && (2.42)\\
&= \frac{e^{-rx} h \overline{\pi} (e^{rx}(r-\mu_-) + e^{x\mu_+}(\mu_- - \mu_+))}{(h+r)(r-\mu_-)(r-\mu_+)} && (2.43)
\end{aligned}$$

which is not so easy to interpret, in particular to check that $V_0 > 0$. When the risk free rate $r = 0$, V_0 simplifies to (multiplying both numerator and denominator by -1)

$$V_0 = \frac{h\overline{\pi}(\mu_- + e^{x\mu_+}(\mu_+ - \mu_-))}{h(-\mu_-)\mu_+}$$

The denominator is positive as $\mu_- < 0 < \mu_+$, and $h > 0$. V_0 is positive when the numerator is positive, i.e., when μ_+ is larger than μ_- enough.

2.9.5 Conclusions

Section 7 covered the application of the Weeds' model to the pharmaceutical industry. The choice of the specific model was driven by considerations in terms of analytical tractability and model settings. In this context important are the assumptions of the model regarding technical uncertainty. Indeed, in the pharmaceutical industry the discovery depends on the probability of success that the project will lead to a finding. This probability of success is expressed in the model by the hazard rate that governs the chances of a discovery taking place.

Other factors governing model selection relate to strategic considerations. The Weeds' model analyzes when it is appropriate to consider a cooperative approach versus a non co-operative one. Strategic alliances are a crucial aspect in the pharmaceutical industry, a sector where innovation and research are the leading drivers. The model settings were considered to be generally appropriate to apply the model and test strategic alliance evidence in the pharmaceutical industry. The results of the study highlighted two main limitations of the model when applied to the pharmaceutical industry. Firstly, the model fails to account for the competence factor; a primary driver in the decision making process for those pursuing business alliances. The second limitation lies in the model's assumption regarding patent value following a Geometric Brownian Motion (GBM) with a unique drift. The unique drift of GBM would cover, improperly, both pre and post patent expiration periods when generics start entering into the market.

This assumption of a unique drift of GBM was replaced in section 9 with a time dependent drift assuming different values post patent expiry. Based on the new assumption an estimation of the impact on the patent's (and firm's) value was performed under three scenarios. These three scenarios summarize a quantification of the effect of a change in the drift parameter. The first scenario represented the benchmark case where the sales dynamic was represented by a GBM with a unique positive drift. This is an unrealistic assumption of the Weed's model when

used in the pharmaceutical business given the sales pattern following patent expiry when generics enter the market.

The second scenario more closely represents the sales dynamics in the pharmaceutical industry: a first period with growing sales up to patent expiry, followed by a second period of decline after the loss of patent exclusivity. This dynamic is expressed by a GBM whose drift is time dependent; exhibiting a positive value up to patent expiry and a negative one after patent expiry.

The third scenario is less common and it is observable only on certain markets such as China in example of Losartan. Here, sales keep showing a stable pattern even after the loss of exclusivity.

The analysis was driven by the aim of understanding the impact on the firm value of a change in the drift assumption. A key finding of the analysis is that changes in drift assumptions underlying the cash flow dynamics have a substantial impact on the value of a firm. Numerical results show the importance of a change in the drift on the firm value. All scenarios show that going from a positive drift of 4% to a negative drift of -4% firm values are heavily reduced. This reduction is particularly important at low levels of h. When h=20%, indicating a low discovery rate, firm value moves from 487 to 58 showing a decline of about 88%. The reduction is slightly lower 74%, firm value goes from 600 to 159 when h=80%. Altogether these results show that a change in the drift has a remarkable impact on the firm value. This implies that the setting of the Weeds model assuming a unique drift can largely overstate the value of the firm.

In conclusion, this study so far finds that the Weeds model, when applied in the pharmaceutical industry, needs further development in order to account for the distinctive dynamics of cash flows following patent expiration of a drug. A model extension is then considered to overcome the limitation implicit in the model assumption of independent cash flows π_s and time of discovery Z. In this context a more realistic approach is to assume that the inverse-V shape of the drifts starts at the time of discovery, instead that at time of firm valuation as stated in the Weed's model. The setting allows finding a firm value in closed form only under specific but relevant cases, namely when cash flows π_z and drift of cash flows μ_u are known, becoming $\bar{\pi}$ and $\bar{\mu}$ respectively. A numerical example shows how the company value changes as function of the growth rate $\bar{\mu}$ and as function of the discovery rate h. The analysis is completed by considering a time dependent drift and patent expiry x years after discovery. Also in this case an expression for the firm value is presented.

The next chapter will explore empirical evidence for the importance of the competence factor when deciding strategic alliances.

Parameters		
σ	10%	
σ^2	1%	volatility
r	10%	exp. return/disc. rate
μ	5%	drift
h	30%	hazard rate
K	0.2	investment costs

Duopoly and Preemption

β_1	5.51	β_0	1.84
$\beta_1 / (\beta_1 - 1)$	1.22		

1a. Follower (F)

B_F 1.48

$V_F(\pi)$	0.01	if $\pi < \pi(F)$
	n.a.	if $\pi \geq \pi(F)$

π_F 0.53

1b. Leader (L)

B_L 6.98

$V_L(\pi)$	0.10	if $\pi < \pi(F)$
	n.a.	if $\pi \geq \pi(F)$

π_L 0.24

2. Joint Investment

B_C 0.26

$V_C(\pi)$	0.05	if $\pi < \pi(C)$
	n.a.	if $\pi \geq \pi(C)$

π_C 0.95

Figure 2.16: Appendix 6a

π_F (discrete steps)	Leader Value	Follower Value	Cooperative investment	NPV - K
0.00	**-0.20**	0.00	0.00	-0.20
0.01	**-0.19**	0.00	0.00	-0.19
0.03	**-0.18**	0.00	0.00	-0.19
0.04	**-0.16**	0.00	0.00	-0.18
0.06	**-0.15**	0.00	0.00	-0.17
0.07	**-0.14**	0.00	0.00	-0.17
0.09	**-0.13**	0.00	0.00	-0.16
0.10	**-0.11**	0.00	0.00	-0.15
0.12	**-0.10**	0.00	0.01	-0.15
0.13	**-0.09**	0.00	0.01	-0.14
0.15	**-0.07**	0.00	0.01	-0.13
0.16	**-0.06**	0.00	0.01	-0.12
0.18	**-0.05**	0.00	0.01	-0.12
0.19	**-0.04**	0.00	0.01	-0.11
0.21	**-0.02**	0.00	0.01	-0.10
0.24	**0.00**	0.00	0.02	-0.09
0.26	**0.02**	0.00	0.02	-0.08
0.28	**0.03**	0.00	0.02	-0.07
0.29	**0.04**	0.00	0.03	-0.07
0.31	**0.05**	0.00	0.03	-0.06
0.32	**0.06**	0.00	0.03	-0.05
0.34	**0.07**	0.00	0.04	-0.04
0.35	**0.08**	0.00	0.04	-0.04
0.37	**0.09**	0.01	0.04	-0.03
0.38	**0.09**	0.01	0.04	-0.02
0.40	**0.10**	0.01	0.05	-0.02
0.41	**0.10**	0.01	0.05	-0.01
0.43	**0.10**	0.01	0.05	0.00
0.44	**0.10**	0.02	0.06	0.00
0.46	**0.10**	0.02	0.06	0.01
0.47	**0.09**	0.02	0.07	0.02
0.49	**0.08**	0.03	0.07	0.03
0.50	**0.07**	0.03	0.07	0.03
0.52	**0.06**	0.04	0.08	0.04
0.53	n.a.	n.a.	0.08	0.05
0.55	n.a.	n.a.	0.09	0.05
0.56	n.a.	n.a.	0.09	0.06
0.58	n.a.	n.a.	0.10	0.07
0.59	n.a.	n.a.	0.10	0.07
0.61	n.a.	n.a.	0.11	0.08
0.63	n.a.	n.a.	0.11	0.09
0.64	n.a.	n.a.	0.12	0.10
0.66	n.a.	n.a.	0.12	0.10
0.67	n.a.	n.a.	0.13	0.11
0.69	n.a.	n.a.	0.13	0.12
0.95	n.a.	n.a.	0.24	0.24
0.96	n.a.	n.a.	0.24	0.24
0.97	n.a.	n.a.	0.25	0.25
0.98	n.a.	n.a.	0.25	0.25
0.95	n.a.	n.a.	0.24	0.24

Note: n.a. values indicatethat the leader andfoller functions are replaced by the project`s NPV after the investment trigger point.

Figure 2.17: Appendix 6b

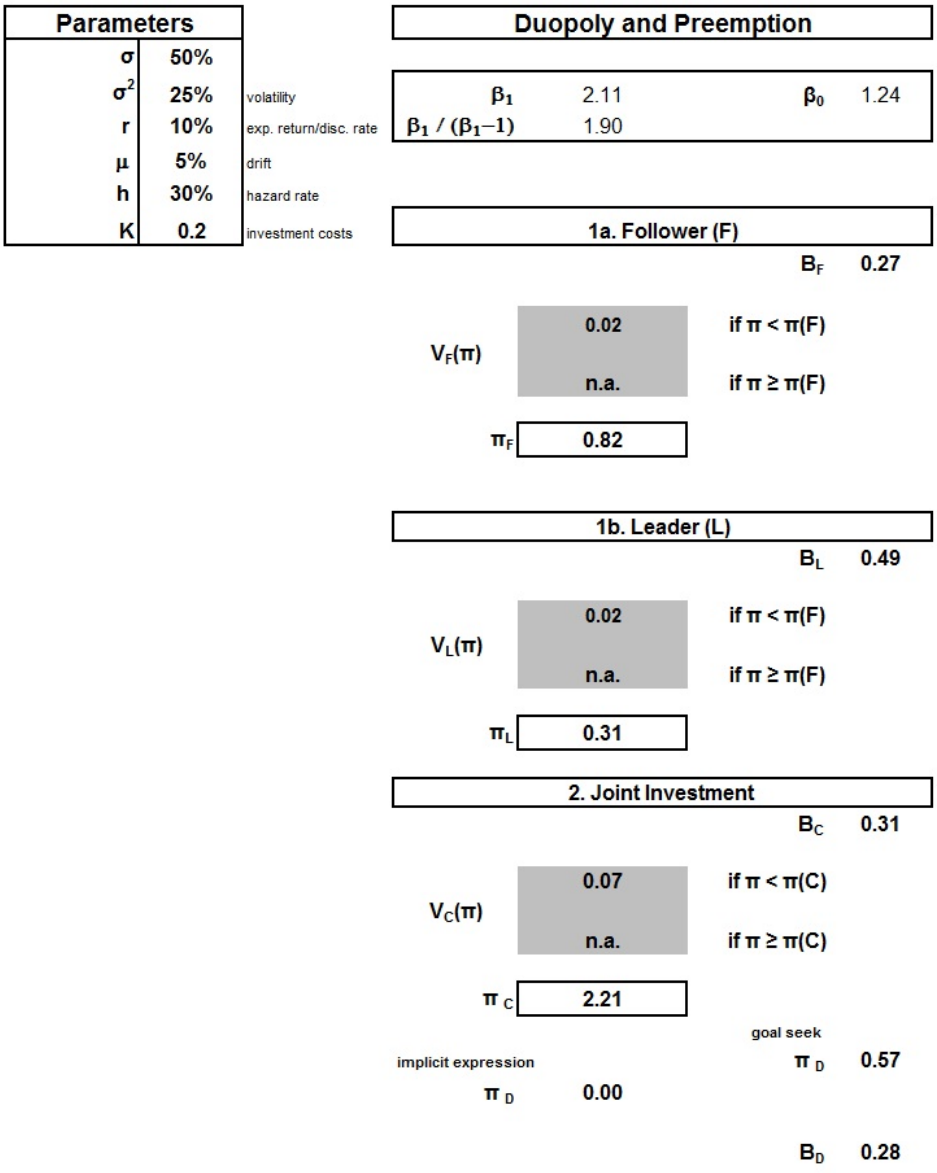

Figure 2.18: Appendix 7a

	$V_L(\pi)$	$V_F(\pi)$	$V_C(\pi)$	
π_F (discrete steps)	Leader Value	Follower Value	Cooperative investment	NPV - K
0.00	-0.20	0.00	0.00	-0.20
0.02	-0.18	0.00	0.00	-0.19
0.04	-0.16	0.00	0.01	-0.18
0.07	-0.15	0.00	0.01	-0.17
0.09	-0.13	0.00	0.02	-0.16
0.11	-0.11	0.00	0.02	-0.15
0.14	-0.09	0.00	0.03	-0.14
0.16	-0.07	0.01	0.03	-0.13
0.18	-0.06	0.01	0.04	-0.12
0.21	-0.04	0.01	0.04	-0.10
0.23	-0.03	0.01	0.05	-0.09
0.25	-0.01	0.01	0.06	-0.08
0.28	0.00	0.02	0.06	-0.07
0.31	0.02	0.02	0.07	-0.06
0.32	0.03	0.03	0.08	-0.05
0.35	0.05	0.03	0.08	-0.04
0.37	0.06	0.03	0.09	-0.03
0.39	0.07	0.04	0.10	-0.02
0.42	0.08	0.04	0.10	-0.01
0.44	0.09	0.05	0.11	0.00
0.46	0.10	0.05	0.12	0.01
0.49	0.11	0.06	0.13	0.03
0.51	0.12	0.07	0.13	0.04
0.54	0.13	0.07	0.14	0.05
0.56	0.14	0.08	0.15	0.06
0.58	0.14	0.09	0.16	0.07
0.61	0.15	0.09	0.16	0.08
0.63	0.15	0.10	0.17	0.09
0.65	0.16	0.11	0.18	0.10
0.68	0.16	0.12	0.19	0.11
0.70	0.17	0.13	0.20	0.12
0.72	0.17	0.14	0.20	0.13
0.75	0.17	0.15	0.21	0.14
0.77	0.18	0.16	0.22	0.16
0.79	0.18	0.17	0.23	0.17
0.82	0.18	0.18	0.24	0.18
0.84	n.a.	n.a.	0.25	0.19
0.86	n.a.	n.a.	0.26	0.20
0.89	n.a.	n.a.	0.26	0.21
0.91	n.a.	n.a.	0.27	0.22
0.93	n.a.	n.a.	0.28	0.23
0.96	n.a.	n.a.	0.29	0.24
0.98	n.a.	n.a.	0.30	0.25
1.01	n.a.	n.a.	0.31	0.26
1.03	n.a.	n.a.	0.32	0.27
1.05	n.a.	n.a.	0.33	0.29
1.08	n.a.	n.a.	0.33	0.30
1.10	n.a.	n.a.	0.34	0.31
1.12	n.a.	n.a.	0.35	0.32
1.15	n.a.	n.a.	0.36	0.33
1.17	n.a.	n.a.	0.37	0.34
1.19	n.a.	n.a.	0.38	0.35
1.22	n.a.	n.a.	0.39	0.36
1.24	n.a.	n.a.	0.40	0.37
1.26	n.a.	n.a.	0.41	0.38
1.29	n.a.	n.a.	0.42	0.39
1.31	n.a.	n.a.	0.43	0.40
1.33	n.a.	n.a.	0.44	0.42
1.36	n.a.	n.a.	0.45	0.43
1.38	n.a.	n.a.	0.46	0.44
1.40	n.a.	n.a.	0.47	0.45
1.43	n.a.	n.a.	0.48	0.46
1.45	n.a.	n.a.	0.49	0.47
1.48	n.a.	n.a.	0.50	0.48
1.50	n.a.	n.a.	0.51	0.49
1.52	n.a.	n.a.	0.52	0.50
1.55	n.a.	n.a.	0.53	0.51
1.57	n.a.	n.a.	0.54	0.52
1.59	n.a.	n.a.	0.55	0.54
1.62	n.a.	n.a.	0.56	0.55
1.64	n.a.	n.a.	0.57	0.56
1.66	n.a.	n.a.	0.58	0.57
1.69	n.a.	n.a.	0.59	0.58
1.71	n.a.	n.a.	0.60	0.59
1.73	n.a.	n.a.	0.61	0.60
1.76	n.a.	n.a.	0.62	0.61
1.78	n.a.	n.a.	0.63	0.62
1.80	n.a.	n.a.	0.63	0.63
1.82	n.a.	n.a.	0.64	0.64
1.84	n.a.	n.a.	0.65	0.65
1.85	n.a.	n.a.	0.66	0.66
1.87	n.a.	n.a.	0.67	0.66
1.91	n.a.	n.a.	0.69	0.68
1.95	n.a.	n.a.	0.70	0.70
1.97	n.a.	n.a.	0.71	0.71
1.99	n.a.	n.a.	0.72	0.72
2.00	n.a.	n.a.	0.73	0.72
2.02	n.a.	n.a.	0.73	0.73
2.04	n.a.	n.a.	0.74	0.74
2.05	n.a.	n.a.	0.75	0.75
2.07	n.a.	n.a.	0.76	0.76
2.09	n.a.	n.a.	0.76	0.76
2.10	n.a.	n.a.	0.77	0.77
2.12	n.a.	n.a.	0.78	0.78
2.14	n.a.	n.a.	0.79	0.79
2.15	n.a.	n.a.	0.79	0.79
2.17	n.a.	n.a.	0.80	0.80
2.18	n.a.	n.a.	0.81	0.81
2.20	n.a.	n.a.	0.82	0.82

Note: n.a. values indicatethat the leader andfoller functions are replaced by the project's NPV after the investment trigger point.

Figure 2.19: Appendix 7b

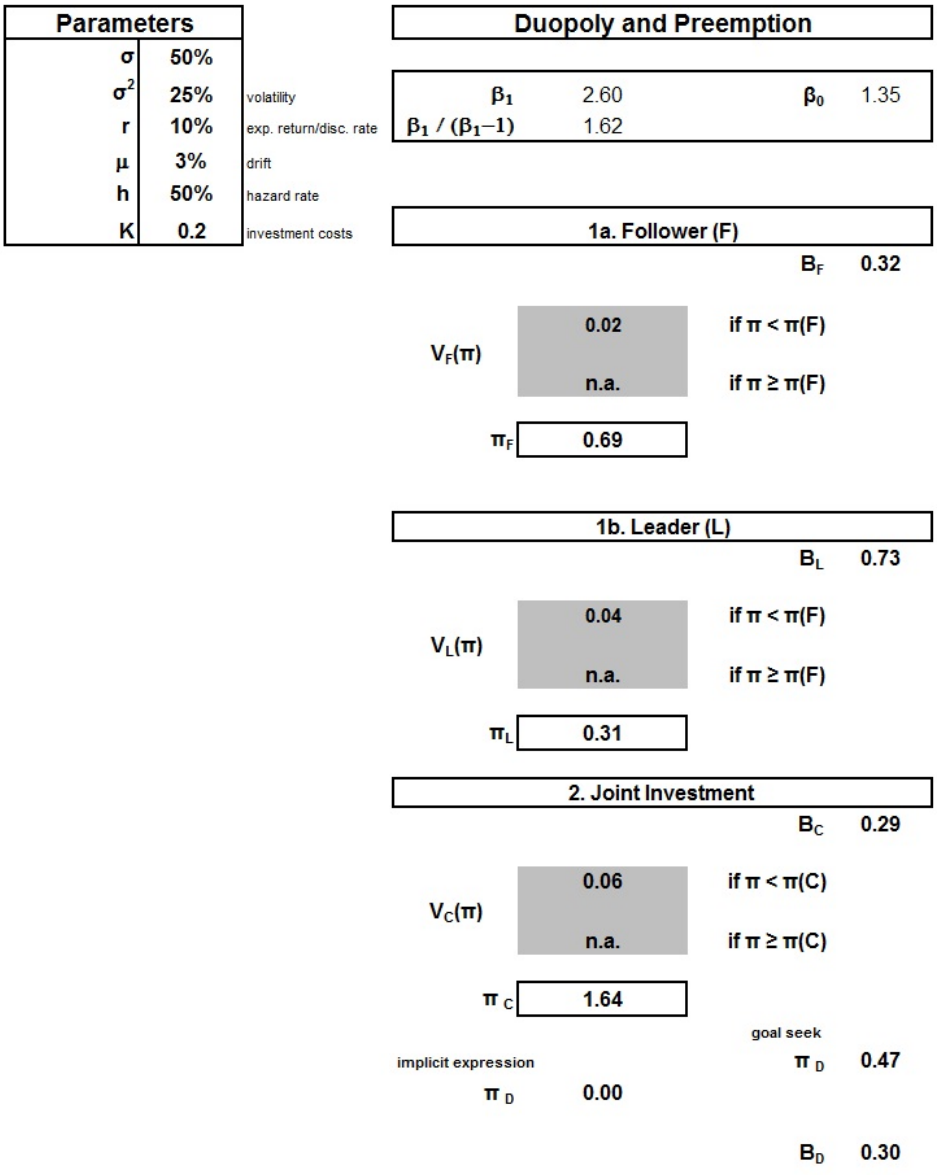

Figure 2.20: Appendix 7c

Chapter 3

Corporate competencies: An empirical application

3.1 Introduction

The previous chapter highlighted the importance of the internal competencies of big pharmaceutical players when making strategic decisions. Of specific importance is the availability of skilled professionals with experience and understanding of a given disease area.

The uniqueness of the pharmaceutical industry, which is itself determined by the number of factors that come into play in clinical trials, makes knowledge and experience about medical research, alongside development and marketing, fundamental assets. Also of key importance are the professional knowledge of scientists, clinicians and marketing professionals as well as best practices. The latter is gained from past experience and aids the identification of the ideal development and marketing conditions for further applications.

In this context, the strategy of a pharmaceutical company defines the focus on a given therapeutic area within which excellence in competencies are developed and retained. In fact, even small turnover rates of key people could cause important losses of knowledge within a given area. The extent to which the company can count on professional excellence in a specific therapeutic area shapes the business strategic alliances. A high level of competent and experienced staff tends to make strategic alliances and cooperation less important. In this case, the company exists within a comfort zone where the primary objective is to gain as much market share as possible so as to exist as a standalone player. The reverse is true when management skills and expertise are limited, making strategic alliances with other players a means of adding

value. The competence factor can be correlated with the notion of speed of learning, a concept developed by Habib and Mella-Barral (2007) in their theoretical work on the role of know-how acquisition in the formation and duration of joint ventures.

After an introduction to the notion of competence factor and a brief description of the main forms of alliances in the pharmaceutical sector, the following sections will attempt to provide empirical evidence of the competence factor within the cardiovascular (CVM) disease area, and the subsequent impact on strategic cooperation. The big pharmaceutical players considered in the analysis are Pfizer and Novartis. These two companies are reputed to have competence excellence in this specific therapeutic area.

3.1.1 The competence factor in the pharmaceutical industry

Core competencies pertaining to the pharmaceutical industry fall under two broad areas: i) R&D, ii) Marketing and Health Authority regulatory approval.

R&D competencies are traditionally related to a new drug discovery. These competencies are extremely important to ensure competitiveness in the market and should be analyzed with reference to the different therapeutic areas within which they are employed. The reason for this is twofold: Firstly, patentable drugs are more easily reached in certain therapeutic areas; secondly the skills and medical knowledge required differ substantially within and between therapeutic areas. For example, new drug research in oncology present peculiarities that are not shown in the discovery of neuroscience drugs. In oncology, when the end point of clinical trials is the measurement of the tumor size, evidence of a drug efficacy is measured in time and its relationship to changes in the size of the tumor. Conversely, a Neuroscience disease, such as Alzheimer's, which has a slow evolution and a mechanism of action which is partially unknown, poses difficulties in defining the end point measurement of success. The process of detecting a drug's efficacy in this area is therefore often longer and more complicated.

In terms of drug discovery, Henderson and Cockburn (1994) identify the portfolio pipeline as one of the main components of the R&D competencies. The other components they identify are the firm's specific scientific knowledge and capabilities. The specific scientific knowledge refers to the highly specialized experience required in areas such as biology, biochemistry, or physiology. All these disciplines constitute a firm's idiosyncratic know-how.

A firm's specific capabilities, as described by Henderson and Cockburn (1994), refer to its external and internal communication abilities. The flow of information to external institu-

tions that play a fundamental part in drug discovery, such universities and research centers, is crucial.

The authors emphasize the importance of such capabilities and measure it in terms of specific conditions which include: the importance of publications within the corporate culture and its relevance to career advancement, the geographical location (i.e. the proximity to academic research centers and medical schools), and the participation around research activities with other academic institutions.

Internal communication refers to a corporate culture of keeping an interdisciplinary approach and the smooth exchange of information from one discipline to the other. Advances made in the last decade in understanding human biology have increased the potential for the discovery of a wide array of new drugs, yet biologists face challenges in translating this knowledge into pharmaceuticals. The complexity of research therefore requires a cross-disciplinary approach where research capabilities are coordinated so as to improve productivity.

Core competencies referring to marketing in the pharmaceutical industry are better understood in the context of a complex and changing pharmaceutical environment. Marketing efforts to meet existing demands require a firm to take on board specific learning processes of adaptation. This holds true for all marketing activities, but specifically for communication and promotion. The new business model is customer value centric and has moved from a mass market to a more targeted approach. Marketing activities must show the added value to the patients, a product amid an array of health services and devices that people are willing to pay a premium for. Customers are represented by patients, healthcare providers and payers such as local health authorities, governments and insurance companies. The role of the payers has become increasingly relevant as key decision makers and the marketing value proposition is adapted to target all stakeholders.

The Health Authority regulatory review requires specific competencies and abilities to deal with the drug approval process. Compliance mechanisms are particularly rigorous and the handling of regulatory requirements necessitates qualified professionals. Dealing with regulatory compliance for drug products means not only understanding the guidelines, but also adopting a practical, operational approach to Health Authority compliance. Knowing how to communicate with the Health Authority, as well as having access to resources and updates on the latest regulations are also key. During the regulatory review, the Health Authority consults medical experts within the specific therapeutic area to garner their opinions on the drug safety and efficacy, with particular attention paid to the content of its labeling. In this respect the

Health Authority might impose a change in the labeling or may even withdraw the product in case of severe contraindication effects provoked by the drug[1]. The approval phase lasts about a year, yet recently this time has tendentially been extended with the increased intensity of data requests by health authorities. Such requests mainly refer to the number of clinical trials demanded and the increasing number of patients employed in each trail. Being able to handle regulatory authority requirements smoothly and expertly means that the product can be launched on the market more quickly. This implies an extension of the product's time under patent protection, and therefore higher profitability.

The analysis of the corporate competences described above reveals how critical they are for maintaining long-term competitive advantage. The competence factor is therefore considered as a source of competitive advantage in response to the evolution of market demand.

3.1.2 The structure of strategic alliances in the life science industry

Strategic alliances form between companies that aim to research, develop or market a drug product cooperatively. Ideally, the two entities combine complementary skills, resources and assets that constitute the basis of the alliance. There are various reasons for strategic alliances to take place including the need to obtain access to new technologies or increase management expertise and skills, the desire to share the risk of a new drug development, or to accelerate the launch and profitability of a product on the market. Financial benefits, which include obtaining cash funds to advance the development of a drug product, are particularly common in alliances involving smaller companies. Biotech firms often form alliances with big players to ensure that their innovative products receive efficient development programs, higher-end marketing support and better commercial venues. Small companies with an interesting portfolio pipeline facing scarce financial resources and marketing skills represent interesting business propositions for big players. In return, a big pharmaceutical company can enter or consolidate its presence in a Therapeutic Area (TA) thus creating and reinforcing its research capabilities. Different forms of alliances are therefore identified based on the resources of one and the objectives of the other.

In a joint venture, the main focus is usually in the R&D of a new drug product. In a research and development joint venture, companies join their resources and capabilities to advance the development of a medicine. The business structure is either in contractual form, or

[1]Source: http://www.fdareview.org/approval_process.shtml

through the creation of a new entity in which the two companies own an equal share. This is the preferred form of agreement in situations where parties want to keep control of the development process while simultaneously sharing the risk of an uncertain and costly project. In order for the joint venture to be successful for both parties, the way the two firms combine their efforts requires special attention. How the joint ventured is managed, the definition of clear roles and responsibilities, and how strategic decisions are made are all extremely important elements.

A production joint venture, while less common than those that focus only on research and development, represents a valuable solution when a firm is at full capacity or when its manufacturing facilities are located too far away from the commercial marketplace.

In recent years there has been a steady increase in the number of collaborations between big pharmaceutical companies and academic institutions[2]. Through such alliances, the pharmaceutical company seeks to gain scientific expertise in a specific Therapeutic Area by providing the academic partner with financial grants. Pharmaceutical companies benefit not only from the research results but also from working with leading academic scientists at the forefront of their research. In comparison to the joint venture, where generally a more balanced relationship in the partnership is pursued, university alliances are characterized by ensuring the extensive freedom of the academic partner. This means that the scientist can decide on the area, the methods and the approach of the research. They have complete autonomy in terms of publishing their research, and in deciding on the kind of information and data to disclose. Yet this freedom can also be a a source of potential conflict. The disclosure of such data to the public might risk exposing a company's development and marketing plans to competitors. When the alliance leads to a successful result and a drug compound is identified, the intellectual property rights are usually retained by the university. Nevertheless, the contract usually ensures that the company retains the right of first refusal to licence the compound.

Under a licence agreement, the licensor transfers the use of Intellectual Property to the licensee according to the contractual terms and conditions which regulate the agreement. Factors such the development, manufacturing and marketing rights, or the agreement's duration, are listed under the terms and conditions which define the various forms of alliances. Some examples of such agreements are: in licence, option deals, co-development, co-marketing and co-promotion.

An in-licence agreement occurs when a proprietary molecule, usually in the early stages

[2]Source: Annual Deal watch 2012 – Medius Associates, www.medius associates.com

of development, is licensed to another firm in exchange for a stream of financial flows which include upfront payments and royalties. The deal signed in 2012 by Galapagos is an example of such an agreement. Here Galapagos, a mid-size biotech company, went into a deal with Abbott laboratories to develop and commercialize a next generation Janus kinase 1 inhibitor in multiple autoimmune disease, receiving $150 million cash upfront. "I am a strong believer that a company should grow expertise", said Dr. Van de Stolpe, Galapagos' CEO. "We are clearly new to this game but the deal was an opportunity to secure some rights. We see this as the opportunity to build the infrastructure for our own product[3]."

More recently, option structures have increasingly been employed in agreements between big pharmaceutical and biotech companies. Contrary to a standard in-licence deal, under the option deal, the big pharmaceutical partner provides the development partner with a limited upfront cash payment (the option price). The option is exercised by the pharmaceutical partner only if certain milestones within the development process are successfully reached by the development partner. The option refers to how certain rights are exercised such as in-licence, the acquisition of specific assets or of the entire company. This business model is well suited to a risk-averse large pharmaceutical company and allows it to hold off payments until successful results are achieved, leaving the development partners (the biotech) to bear most of the development risk.

Co-development agreements involve the development of a product by two firms that share both the costs and the development activities. The agreement can cover various phases of the development process, even if co-developments of early phases such phase 2a and 2b are more frequent.

In co-marketing agreements, the drug product is marketed by both companies under their own trading names. The company that owns the product grants the partner the right to market the product in exchange for royalties and possibly upfront payments. All marketing activity is usually focused on specific geographical markets which are defined by the owner's strategy; global co-marketing agreements are less common. One example of how co-marketing works is found in the agreement that was signed between UCB and Novartis in 2009, when UCB was looking to expand into cardiovascular and diabetes products in the German market. " With this agreement UCB aims to extend the product line for the treatment of hypertension and at the same time enter the growing diabetes market with new oral anti diabetics extending our

[3]Script Intelligence 29 February 2012 –Galapagos lands $150M bounty in $1.35bn autoimmune deal with Abbott-Mike Ward and John Hodgson.

cardiovascular and metabolic product portfolio with the most attractive and innovative treatment option to date, in line with UCB's ambition to offer the best medicines to our patients[4]", said Willy Cnops, Vice President UCB and Managing Director Germany.

A co-marketing agreement should be based on synergies in product sales strategies. However, risk can arise from competition generated between the sales forces of the two companies, and the costs that are implied.

In a co-promotion contract, the drug product is promoted by both companies using the same trading name. This contract works well for products with high market potential and for which investing heavily in sales promotion is a safe and sound strategy. For this reason drugs for rare diseases or over the counter products are not co-promoted. Co-promotion agreements should lead to economic benefits that include reduced competition, the exchange of professional competencies, economies of scale in production and higher market penetration. Success relies on a variety of critical factors which include the coordination of sales forces to target different groups of doctors, a similarity in the corporate culture and marketing style of the two partners, and a clearly identified marketing message.

3.2 The role of the competence factor in the formation and duration of strategic alliances

This study aims at providing empirical evidence which will highlight the importance of internal competencies when making strategic decisions in the pharmaceutical industry. Various authors have explored the potential associated with building strategic alliances in order to acquire new competencies. Cohen and Levinthal (1990) considered the role of "absorptive capacity" in decisions to participate in cooperative R&D ventures. Absorptive capacity is defined as the "ability of a firm to recognize the value of new, external information, assimilate it and apply it to commercial ends ". Doz (1996) went on to show how value is added to this learning process which moves along cycles that correspond in parallel to the various phases of the alliance. In this respect the author identifies successful alliances as those that are "highly evolutionary" and characterized by several learning cycles, while less successful co-operations are inertial and involve little learning.

Along similar lines, Iyer (2002) proposed that the learning factor represents the primary incentive to form alliances and that learning evolves during the alliance's lifecycle. The author

[4]Published on FierceBiotech (http://www.fiercebiotech.com)

goes on to identify some of the learning behavior used to acquire knowledge in the context of alliance evolution. For example, in the initial phase of an alliance learning mechanisms are unilateral, with companies trying to learn about strategic skills and competencies of the potential partner. Conversely later phases of an alliance are characterized by mutual learning processes involving substantial information exchanges. This is the phase where partners' experiences and skills are cumulated to improve productivity.

Some authors (Khanna, Gulati and Nohria, 1998) take this principle a step further by exploring those learning alliances, defined as agreements, where the main goal of both partners is to learn from each other. Yoshiro and Rangan (1995) take an even more extreme positions by claiming that every firm considers learning to be the strategic objective in an alliance. Hamel (1991), through an analysis which included management interviews of nine internal alliances, focused on the determinants of inter-partner learning. The author concludes that there are asymmetries in learning, with different partners showing different capabilities in terms of learning. Szulanski, (1996) identified the principle of "internal stickness" which is an inability to transfer knowledge and best practices within a firm, which ultimately compromises the chances of entering into successful strategic alliances and partnerships.

Some authors make specific reference to the pharmaceutical and biotech industry. For example, Patzelt, Shepherd, Deeds and Bradley (2008) focused their analysis on the German biotech industry. The authors assert that entering into a new alliance allows companies to gain previously missing competencies, and that this is interpreted in terms of the partner's financial resources. They state that a situation of 'financial slack' would encourage management to make the strategic decision to acquire missing capabilities through alliances. Here, financial slack can either enhance the desire of the business partner to compensate its perceived lack of competence, or it acts as the resource that allows the utilization of the acquired competencies.

Coombs et al., (2006) indicate that in the biotech area, alliances are established mainly to obtain financial resources and analyzed the dynamics of the financial resources between partners. The authors identify specific factors, such as quality science, as determinants for domestic alliance partnerships, while other factors, such as location, are explanatory of foreign alliance partners. A resource-based approach is used by Das and Teng (2000) to examine strategic alliances. A specific example is used to identify how financial and marketing competencies are the resources most often provided by big pharmaceutical companies when allying with small biotech.

In general, research to date on strategic alliances has focused more on learning dynam-

ics and the transfer of knowledge within a static model approach. Consequently less is understood about the role of the competence factor from a temporal dimension. Very little is therefore known about the conditions under which a joint venture is created, and dissolved, and at which point in time this happens. An important step towards closing this knowledge gap was achieved by Habib and Mella-Barral (2007). Using a continuous time model the authors analyzed the dynamic nature of knowledge acquisitions in the formation and duration of joint ventures, while considering the evolution of the joint ventures over time. They went on to identify the factors that incentivize the formation of joint ventures and modeled the benefits that each partner gains from a business alliance. The knowhow factor is considered a key element throughout the lifecycle of joint ventures; from the initial decision to start, to the final decision to dissolve the partnership. Indeed, if the possibility of gaining knowhow is a key determinant in the formation of a joint venture, the same factor plays a crucial role in the decision to terminate it. The authors focused particularly on the conclusion of the joint venture; the conditions, the timings and the role played by the knowhow factor in this phase. They concluded that parties only enter into alliances when there is a perception of mutual benefit. The dynamics of knowhow acquisition is such that the partner that most efficiently captures the shared knowledge buys out the other partner, thus determining the dissolution of the joint venture. Each joint venture is therefore temporary. In this respect, the assumption is that "as each partners' knowhow increases, so does the partner's ability to operate the asset separately". The increase in a partner's knowhow is uncertain and dependent on how favorable the learning conditions are within the joint venture. The latter is modeled by a geometric Brownian motion. It finds that an increase in learning conditions expressed by a higher drift of the stochastic process, decreases the duration of the joint venture. Conversely an increase in the volatility of learning conditions, making the option to dissolve the joint venture more valuable, increases the duration of the joint venture. Other comparative statics results support the finding that the more knowhow available for the buying partner, the longer they want to stay in the alliance, thus increasing the duration of the joint venture. At the same time, the higher the speed of learning of the buying partner in acquiring knowhow, the shorter the duration of the joint venture.

3.3 Empirical evidence of the competence factor

Spanning from January 2000 to September 2011, the study is based on almost eleven years of monthly sales (IMS source). It includes monthly volumes for both Pfizer and Novartis and "All Other" players that define the CVM market with reference to the Hypertension indication.

The exploratory analysis of the data is performed into two steps. The first part considers the time series of the ratios for the CVM market players: Pfizer, Novartis and All Others. The ratios of each player's sales and volumes in units (defined below as (3.1) and (3.2)) are taken as a proxy for the specific skills, strengths and experiences that define the competence factor. The choice of the ratios are determined by a specific reason . The amount of sales and volumes are affected not only by the company's skills, but by many other factors such as exchange rates, economic conditions, business cycle, and technology. To neutralize the impact of these other factors a ratio over the total sales has been selected. Arguably, this ratio is a better reflection of the skill or competence factor.

$$\frac{\$ \text{ Sales}_{i,t}}{\$ \text{ Total Sales}} \tag{3.1}$$

$$\frac{\text{unit Sales}_{i,t}}{\text{unit Total Sales}} \tag{3.2}$$

where $i =$ Pfizer, Novartis, All Others and $t =$ time in months.

Line graphs of the ratios highlight the changes over time. In any one specific case is also important to understand the trend of sales across years.

In figure 3.1, the dashed line, representing the sales ratio of Pfizer, indicates a declining trend, particularly after 2006 when the blockbuster Norvasc went off-patent. At this time, sales of Novartis (the dotted line) outperformed those of Pfizer in the hypertension indication, and show a steady increasing trend since the launch in 1998 of its blockbuster hypertension treatment Diovan. The trend further increases in 2008 when Exforge, a combination drug of Diovan (or co-Diovan) , was launched on the market by Novartis. The remaining part of the hypertension market is represented by "All Other" players, and includes several generics, and shows a slight tendency to increase. Pfizer and Novartis together represent about 27% of the total market in dollars, and about 17% in terms of volumes (units). The higher percentage in terms of dollars is due to the higher price of the branded products in respect to the cheaper generic products that make up "All Others" .

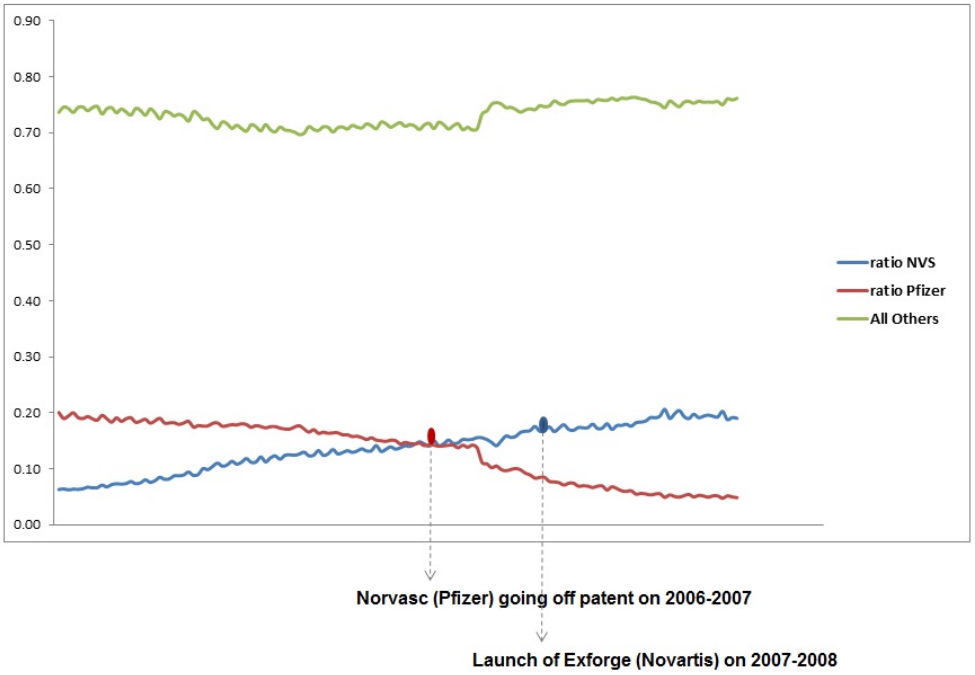

Figure 3.1: Time series of sales ratios. Source: IMS data base

The second part of the exploratory analysis compares the means of the two players Pfizer and Novartis on one side, and "All Others" on the other. The comparison of means is performed for both sets of sales and volumes ratios, as shown below in (3.3) and (3.4).

$$\frac{\$\ \text{Sales}_t}{\$\ \text{Total Sales}} = \frac{\$\ \text{Sales Pfizer}_t}{\$\ \text{Total Sales}} + \frac{\$\ \text{Sales Novartis}_t}{\$\ \text{Total Sales}} \tag{3.3}$$

$$\frac{\text{unit Sales}_t}{\text{unit Total Sales}} = \frac{\text{unit Sales Pfizer}_t}{\text{unit Total Sales}} + \frac{\text{unit Sales Novartis}_t}{\text{unit Total Sales}} \tag{3.4}$$

The comparison of the means is performed by using a standard Hypothesis test about the means:

H_0 : mean1 =mean2

H_1 : mean1 $\neq$ mean2

where mean1 represents the mean of the times series of the Pfizer and Novartis ratios summed together, as per (3.3) and (3.4). Conversely mean2 represents the mean of the ratios of "All Others". The F tests is performed at the 99% significance level over various period of time.

The first period of time is the whole set from 2000 to 2011. The results of the F test,

with 1 degree of freedom at the numerator and 282 at the denominator, are such that the null hypothesis H_0 is rejected. This leads to the conclusion that a significant difference exists in the sum of means of Pfizer and Novartis and "All Others".

The F test rejects the null hypothesis for both sales and volumes, reinforcing the conclusion that the means originate from different populations.

To assess the robustness of these results, a subsample analysis is performed. The aim is to identify significant period of time, as identified by significant events. The F tests are repeated for the sub-periods and confirm the robustness of the results.

As previously identified, there are two critical events that led to the definition of three time periods. The first happened on June 2006 when Pfizer's blockbuster drug Norvasc starts going off-patent, thus triggering a reduction of sales. The second event is represented by the first launch of the combination product Exforge by Novartis at the end of 2007. The third event is the launch in various markets of Exforge and the consequent boost in sales trend. The corresponding time periods are as follows:

1) From Jan. 2000 to June 2006

2) From Jul. 2006 to Dec. 2007

3) From Jan. 2008 to Sep. 2011

All three sub periods are represented in this analysis with the F tests calculations. The results are consistent and suggest the rejection of the null hypothesis H_0. This statistical evidence shows a significant difference between the sum of means of Pfizer and Novartis together and "All Others" which will next be interpreted in business terms. The ratios of each player's sales and volumes are taken as a proxy for the competence excellence factor. Therefore, the statistical results suggest that the two big players, Pfizer and Novartis, show a factor of competence excellence significantly different from the "All Others" players in the market.

The next step in the analysis relates to the possibility of finding statistical evidence around the probability of pursuing a cooperative strategy. This means that the probability of making business agreements (licensing and in general cooperation deals) should show a decreasing trend when the competence factor is increasing. In this context, ratios of sales (as defined above in (3.1)) are again taken as a proxy[5] of the competence factor.

[5]The ratio of sales expressed in dollars best captures the nominal effect due to pricing and macroeconomic factors such as inflation

3.4 Statistical evidence of a cooperative strategy

The variable of interest (deal or no deal) is modelled as a binary variable outcome that can take only two values: either one or zero. The dependent variable y is a qualitative variable and indicates whether a cooperative deal has been signed or not. Specifically, $y = 1$ means that the outcome cooperation deal has been signed, whereas $y = 0$ means that no deal is signed. The dependent variable is then regressed on the explanatory variable.

The standard linear regression model for y would be $y_i = x_i'\beta + \epsilon_i, \forall i$, with $x_i'\beta = \beta_0 + \tilde{x_i}\beta_1$, where $\tilde{x_i}$ represents the proxy for the competence factor, β_0 is a constant and β_1 measures the impact of the competence factor on the probability of making a deal. The model can be written in term of expectation operator as:

$$E[y_i|x_i] = x_i'\beta$$

for some explanatory variable x_i' and parameter vector β.

In the simplest model the probability of success (the event cooperation deal is going ahead), is given by p under the following Bernoulli scheme:

$$y_i = \begin{cases} 1 & \text{probability} \quad p \\ 0 & \text{probability} \quad 1-p \end{cases} \quad \text{and} \quad E[y_i] = p$$

Under this model if the probability of concluding a deal depends for example on the competence factor x_i of parties involved, then p should depend on x_i. As probability of success is the same as the expected value of y

$$E[y_i|x_i] = p(x_i) = x_i'\beta \tag{3.5}$$

The conditional mean of y_i is the conditional probability that the company signs a deal. The set of parameters β represent the impact of the regressors x on the probability. The model defined by equation (3.5) above implies that the probability of success $p(x_i)$ is a linear function of x_i.

The linear regression model, with a binary dependent variable, is defined by the (LPM) Linear probability model (Wooldridge 2006). Estimating the LPM model via least squares has two main drawbacks: it can produce probabilities that are outside the interval $[0, 1]$ and is not based on a maximum likelihood estimator as the errors are not normally distributed. Both

drawbacks are overcome by using suitable binary response models: the Logit and Probit models.

3.4.1 The Logit model

To compensate for the LPM limitations, the Logit model considers a class of binary response models in the form of:

$$E[y_i|x_i] = p(x_i) = f(x_i'\beta),$$

where f is a logistic function in the form of $f(x_i'\beta) = \frac{e^{x_i'\beta}}{1+e^{x_i'\beta}}$ taking on values strictly between zero and one. This automatically ensures that the estimated probabilities of making a deal are inside the interval $[0, 1]$.

Similarly the cumulative Normal distribution can be used, i.e. $f(x_i'\beta) = \int_{-\infty}^{x_i'\beta} \varphi(t)dt$, giving rise to the Probit model, where $\varphi(t)$ is the normal density function.

Unlike the linear probability model, the estimation of the Logit and Probit model is based on the method of maximum likelihood (Greene 2008).

Conditionally on the regressors, the model with success probability $P(y_i = 1)$ assumes independent observation (and therefore probabilities) and leads to the likelihood function:

$$\text{Likelihood}(\beta) = P(y_1 = 1)P(y_2 = 0)\cdots P(y_n = 0),$$

when the sequence of observed dependent variables is $1, 0, \ldots, 0$. For example in the Logit model the Likelihood function takes the form

$$\text{Likelihood}(\beta) = \prod_{y_i=1} \frac{e^{x_i'\beta}}{1+e^{x_i'\beta}} \prod_{y_i=0} \left(1 - \frac{e^{x_i'\beta}}{1+e^{x_i'\beta}}\right)$$

That is the likelihood that the product of the Logit function for those "deal event" occurring multiplied by the product of one minus the Logit function for those "no deal event" occurring.

By maximizing the likelihood function (ML) with respect to the vector β, the Logit coefficient $\hat{\beta}_{\text{MLE}}$ is estimated . This suggests that the probability of signing a deal for company i predicted by the model is given by:

$$\frac{e^{x_i'\beta_{\text{MLE}}}}{1+e^{x_i'\beta_{\text{MLE}}}} = \frac{e^{\beta_0+\beta_1\tilde{x}_i}}{1+e^{\beta_0+\beta_1\tilde{x}_i}}$$

Given the difficulty of justifying the choice of one distribution or another on the basis of a theoretical discussion, both models will be considered in the analysis. The fitting performance of the model will determine the decision to favour the Logit versus the Probit model.

3.4.2 Analysis of the data

The statistical evidence is based on the assumption that the ratios of sales (as defined in eq. (3.1) are a proxy for the competence factor. Various factors (such as strategic or future outlook, for example) enter into play when the decision to embark on a deal is taken. Among these factors, the competence parameter is considered the most prominent.

To proceed with the analysis, the monthly ratios of Novartis sales over total sales are first considered. The averages of ratios for each semester are next calculated and used as a reference. The analysis covers the period 2003-2011, or 18 semesters of data.

The next step is to consider the number of deals, per semester, performed between 2003 and 2011 in the Hypertension market. This is considered as the number of deals that could potentially be signed by a company in the CVM area. Based on the Pharma Deals database, this number of potential deals varies from a minimum of 16 in 2007 (or 8 deals per semester) to a maximum of 28 (or 14 per semester) in 2010. The last piece of information is represented by the deals signed by Novartis over the same period which amount to 10, whereas the number of deals signed by Pfizer over the same period is only 4. The challenge represented by the limited amount of deals by Pfizer forces the decision to take Novartis as reference. The total deals signed per semester divided by the number of potential deals represents the proportion or percentage frequency of deals.

In this context, it is important to notice that 10 deals represents a small set of data when considered against the total potential deals on the whole hypertensive market. This implies that the proportion of deals represented by the Novartis sample does not reach one (or 100%) .

Both models (Logit and Probit) are considered but, the best fit is obtained by the Logit model. As previously discussed, there is no absolute criteria for choosing one model versus the other, but in this case the asymmetry of the deals' distribution could explain why a logistic function fits the data better than a symmetric normal.

The scatter plot in figure 3.2 is a graphic representation of the Logit model predictions. The x axis represents the sales ratios (taken as proxy of the competence factor) while the y axis represents the proportion, or frequency, of deals. The dots represent sample observations and

correspond to the values of the dependent dummy variable equal to zero, when no deals were signed, and values different to zero, when a certain number of deals was signed. In this respect, notice how the proportion of deals signed by Novartis is always below 20%. An exception is represented by the observation on the top of the graph showing a higher proportion of about 33%[6]. The fitted values are represented by the regression line whose beta parameters are:

Intercept= 2.9

Slope= -40

The corresponding t statistics are:

Intercept= 1.3

Slope= -2.5

The slope coefficient of the comptetence factor is statistically significant.

The negative slope of the fitted model expresses a negative relationship between the probability of signing a deal and the competence factor (whose proxy is represented by the ratio of sales). This can be interpreted in business terms as evidence that when the competence factor increases, the probability of making deals decreases. This means that companies that are particularly strong in term of skill and competence, within the Hypertension disease area, tend not to enter into cooperation agreements. It can be inferred from the fitted model that the probability of Novartis to close a deal reaches a high percentage only when the competence factor tends to very low value.

Unreported estimation results of the probit model detected and analogous negative relation between the probability of signing a deal and the competence factor. This funding further supports the empirical evidence above.

3.4.3 The economic impact

A closer look at the statistics concerning the number of deals reveals that the average number of deals signed is $y = 6\%$. This means that "unconditionally" for every 100 potential deals, the company signs 6. A low figure such as this reflects the strength of a company's position within the Hypertensive market. That only a few deals were signed indicates the high level of significance of those few deals to the company. Considering the average "conditional" deals signed is of particular relevance in this situation, since such deals are conditional to the presence of a certain level of competence.

[6]In the specific case three deals (of which two were local small deals) were signed by Novartis over a total of nine signed that semester on the overall market.

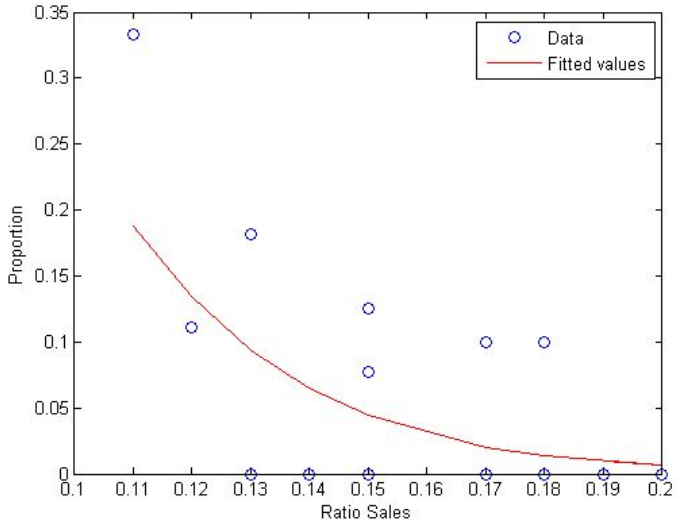

Figure 3.2: Scatter Plot-Logit model

The Logit model identifies the negative relationship between a company's competence factor and its propensity to implement a cooperative strategy. The function is not linear in x and therefore it becomes difficult to interpret the parameter β and draw conclusions about its value. It is therefore particularly important to analyse the impact of a percentage change in the competence factor over the probability of making deals. This will reveal the percentage decrease in the probability of making a deal that is driven by a % increase in the competence factor.

In the standard linear regression model, $y_i = \beta_0 + \tilde{x_i}\beta_1 + \epsilon_i$, the parameter β can be interpreted in terms of derivative:

$$E[y_i|x_i] = \beta_0 + \beta_1\tilde{x_i}$$

$$\frac{\partial E[y_i|\tilde{x_i}]}{\partial x_i} = \beta_1$$

That is, the change in probability is given by the partial derivative with respect to $\tilde{x_i}$.

In the Logit model, the partial derivative becomes:

$$\beta_1 e^{x_i'\beta}(1 + e^{x_i'\beta})^{-2} \tag{3.6}$$

The change in x, the competence factor, leads to a corresponding change in y, the probability of making a deal. In this case, instead of considering the change in the explanatory

variable x in terms of units, it is more appropriate to consider the change in terms of standard deviations (SD) . This is because a change of one unit can be difficult to interpret economically. It is therefore more appropriate to consider a change in relative terms using standard deviation.

Given expression (3.6), it is evident that the economic effect varies for each value of the explanatory variable. A common way to estimate the impact is to use the average values of the explanatory variable (Kennedy 2008).

In this case, the average value $\bar{x}$ is 0.16 while the SD of x is 0.03. The standard deviation represents the average deviation, therefore each time the x value is increased by one unit of SD, the Logit model gives the average change in y. In this study, the average change in y, the probability of making deals, is equal to -0.0271, or -2.7%. This means that each time the competence factor is increased by a unit of average deviation, the probability of signing a deal decreases by 2.7%, which is an economically sizeable decrease.

3.4.4 The Logit model and the linear regression

The previous section recalled the theoretical drawbacks of the linear regression as compared to the Logit model in fitting the response values. To compare the two empirically, it is useful to show how linear regression is displayed in the same scatter plot as the Logit model, as shown in fig 3.3. The scatter plot shows an important limitation of the linear regression model: for high values of x, the regression line becomes negative, thus implying assuming negative probability values. In other words the prediction of the linear model is not suitable to represent probability values whose range span lies in the interval $[0, 1]$.

3.5 Summary and conclusions

This chapter has provided empirical evidence to highlight the various determinants of cooperation strategies among big players in the pharmaceutical business. In an industry led by innovation, the cooperative model can only be the preferred method under specific conditions where the internal competences of a firm in each disease area play a crucial role. Excellence in competence is seen as the availability of skilled researchers in medical discovery together with experts in development and marketing. When those skill factors are present, the firm is less willing to pursue strategic alliances and is more inclined to seek and defend a larger market share as a standalone player.

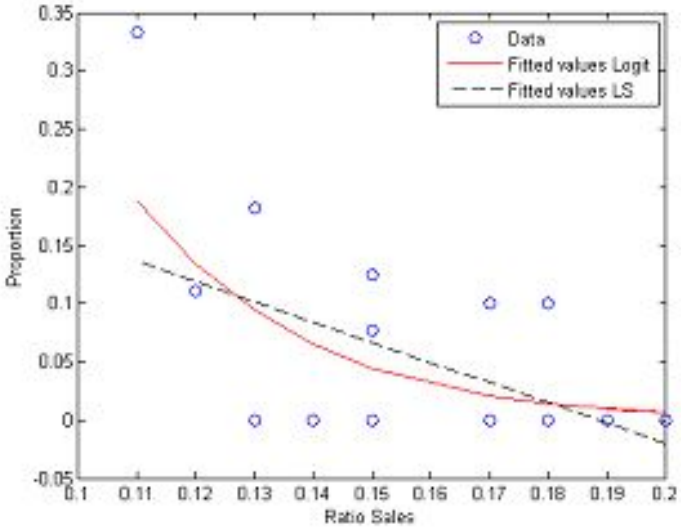

Figure 3.3: Scatter Plot-Logit model and Linear regression model

Empirical evidence of competence factor was analysed in the hypertensive disease area by considering the two biggest market players: Pfizer and Novartis.

The first step in the analysis revealed statistical results that support the evidence of a competence excellence factor within the two players.

The second step of the analysis identified the probability of pursuing a cooperative strategy by signing a deal. In this context, the Logit model was employed to overcome the limitations of a linear regression model. In the Logit model, the identification and quantification of the impact of the competence factor on the probability of making a deal was explored. By analysing the deals signed in the Hypertensive market between 2003-2010, a key finding was that the relationship between the probability of signing a deal (the dependent variable) and the competence factor (the explanatory variable), is negative. This supports the view that high levels of competence are important factors when considering cooperation and business alliance strategies. In this perspective, calculating the economic impact quantifies the effect of increases in the competence factor, which leads to a corresponding decrease in the probability of pursuing business cooperation by signing a deal.

The results outlined are broadly consistent with the theoretical prediction of Habib and Mella-Barral (2007). A key variable in their setting is the speed of learning that one could argue is correlated to the competence factor. According to the authors the knowhow acquisition plays a crucial role in creating and dissolving joint ventures, and alliances are seen as a mean for transferring know how. In this context a key finding is that the faster the speed of learning

the shorter the duration of the joint venture. Consequently the joint venture is dissolved once the desired competencies have been transferred.

Today, the discovery and development processes of pharmaceutical drugs are going through rapid changes and pharmaceutical firms must maintain the flow of innovation in order to ensure survival and growth. Where such firms can count on the flow of in-house discoveries and marketing skills, they will enjoy higher market achievements. Therefore, more than ever, future success is linked to the development and consolidation of core competencies in discovery, development and marketing.

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QUALIFICATIONS

2006 - 2014 **University of Zurich -** CH - PhD program in Banking and Finance – magna cum laude
2009 - 2010 **Fitch Group London -** UK – CQF: Certificate in Quantitative Finance
1997 - 1998 **University of Chicago -** USA- Master in Business Administration
1995 **University of Bologna -** CPA **-** Chartered Professional Accountant and Auditor
1983 - 1988 **Bocconi University -** Milan - Degree in Business Administration - Quantitative methods

PROFESSIONAL EXPERIENCE

2013- current **Novartis International.** - Basel
IR Head of Back Office
Group Investor Relations
- Back office responsibilities: Quarterly external financial reporting, external reporting on M&A projects, full year results reporting managing across functional areas

2012- 2013 **Novartis International** - Basel
Senior Financial Manager
Group Capital Markets
- Responsible for implementing the Tri-party Reverse Repo as financial instrument to reduce counter-party credit risk. Selected and managed the relationship with the Clearing House
- Negotiated the GMRA contract with the most important global Investment Banks

2010-2011 **Senior Portfolio Manager**
Group Portfolio Management
- Responsible for financial valuation of company's products pipeline
- Developed and implemented quantitative models for the measurement of projects' probabilities of success

2006-2010 **Senior Finance Manager**
Business Development Finance
- Responsible for financial and business evaluation of in-licensing, out-licensing and divestment deals.
- Finalized about 75 deals (local and global), of which 5 signed

2000-2005 **ABB Ltd.** - Zurich
Group -Assistant Vice president
Corporate Strategic Finance
- Fully responsible for valuation models in the ABB group, including M&A, and Capital Budgeting valuation models. Also managed business valuation support for M&A and Corporate Financial Strategy departments

1999 - 2000 **Fiat Ges. Co. SPA.** - Turin- Italy
Financial Manager
M&A and Corporate finance
- Missions: Participating in the acquisition project of the Pico Group (USA)
- Group evaluation analysis with definition of quantitative and strategic issues

1993 - 1997 **Court of Justice of Reggio Emilia** - Italy
Company evaluation Advisor
- Responsibilities: defining economic causes of bankruptcies including company evaluation of equity and debt position

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